UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

IN RE NEURONTIN MARKETING, SALES PRACTICES, AND PRODUCTS LIABILITY LITIGATION	)	
THIS DOCUMENT RELATES TO:	)	MDL NO. 1629 CIVIL ACTION NO.
ALL PRODUCTS LIABILITY ACTIONS	)	04-10981-PBS

MEMORANDUM AND ORDER

May 5, 2009

Saris, U.S.D.J.

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I. INTRODUCTION

In these products liability cases, Plaintiffs allege that they, or their decedents, suffered suicide-related injuries when their doctors prescribed the drug Neurontin, manufactured by defendants Pfizer and Warner-Lambert Company ("Defendants").[1] Specifically, they allege that Neurontin caused behavioral disturbances, depression, and ultimately suicidal actions (including completed suicide) in over one hundred individuals. Defendants have moved to exclude Plaintiffs' expert testimony on the issue of general causation – that is, the question of whether Neurontin has the capacity to cause the alleged suicide-related events (suicide attempt, gesture, ideation, and/or completed suicide). (Docket No. 1157.)

After a three-day hearing,[2] conducted jointly with Justice Marcy S. Friedman of the New York State Supreme Court,[3] and

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[1] Pfizer acquired Warner-Lambert in 2000.

[2] The hearing began with two days of argument and testimony on June 19 and 20, 2008. The hearing was then continued until July 23, 2008, when the Court reconvened for a third and final day.

[3] The importance of coordination of related claims in federal and state litigations has increasingly been recognized. (Manual for Complex Litigation (Fourth) § 20 (2004)). The joint hearing was held in furtherance of this goal and with a view to reducing costs, delays, and duplication of effort. (See id. at § 20.31.) In addition, with the knowledge and consent of the parties, the federal and state courts have conferred on the issues raised in the Frye/Daubert hearing.

This Court is advised that the state court will issue a separate opinion adopting this Court's analysis of and findings on the reliability of Plaintiffs' methodology and conclusions on

review of the voluminous briefing and submissions,[4] the motion is **DENIED**.

II. BACKGROUND

A. A Brief History of Neurontin Litigation

Defendants manufacture and distribute the prescription drug Neurontin, or gabapentin (generic).[5] In December 1993, the Food and Drug Administration ("FDA") approved Neurontin for use as an "adjunctive therapy" (i.e., second-line treatment) in the treatment of partial seizures in adults with epilepsy. See In re Neurontin Mktg. and Sale Practices Litig., 244 F.R.D. 89, 92 (D. Mass. 2007). In May 2002, the FDA approved Neurontin for the management of post-herpetic neuralgia (pain resulting from nerve damage caused by shingles or herpes zoster) in adults. Id. In the late 1980s and early 1990s, Parke-Davis, a division of Warner-Lambert, filed patent applications for Neurontin as a

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the issue of general causation.

[4] Plaintiffs and Defendants each submitted hundreds of exhibits through declarations accompanying their respective legal memoranda. All exhibits submitted by Plaintiffs with the Declaration of Andrew G. Finkelstein to Plaintiffs' Memorandum in Opposition to Defendants' Motion to Exclude (Docket No. 1197) will be cited as "Pls.' Ex. __." All Plaintiffs' exhibits submitted with the Declaration of Andrew G. Finkelstein to Plaintiffs' Sur-Reply Memorandum (Docket No. 1255) will be cited as "Pls.' Sur-Reply Ex. __." Similarly, all Defendants' exhibits submitted with the Declaration of Scott Sayler in support of Defendants' Motion to Exclude (Docket No. 1160) will be cited as "Defs.' Ex. __."

[5] Gabapentin is the generic name for Neurontin. Both names (gabapentin and Neurontin) will be used in this opinion.

treatment for depression, neurodegenerative disease, mania, and bipolar disorder; Parke-Davis, however, never sought FDA-approval for any of these indications. Id. Without FDA approval of Neurontin for indications beyond epilepsy and post-herpetic neuralgia, the law prohibited Defendants from marketing or promoting Neurontin for other ("off-label") uses.[6] Id.

As this Court detailed extensively in a prior opinion, Defendants face allegations that they nevertheless engaged in an extensive off-label marketing scheme, promoting Neurontin for a variety of off-label uses, including psychiatric disorders such as bipolar, mood, and anxiety disorders. See id. at 92-103 (detailing the alleged off-label marketing scheme). In July 2004, Defendants pled guilty to two criminal counts related to the off-label marketing and misbranding of Neurontin. Civil actions were filed in federal courts across the country, all of which have been consolidated into the multi-district litigation presently before this Court. The Neurontin multi-district litigation has two distinct parts: (1) "Sales and Marketing" actions brought by consumer purchasers and third party payors for damages stemming from Defendants' alleged fraudulent off-label marketing scheme and (2) "Products Liability" actions alleging injuries resulting from the prescription and subsequent use of Neurontin. The current motion relates to the products liability

[6] Doctors, however, are permitted to prescribe a drug for uses beyond FDA approval. Id.

actions alleging suicide-related injuries caused by Neurontin.

B. The Legal Backdrop and the Current Motion

In order to prevail in a pharmaceutical personal injury case, a plaintiff must establish two types of causation: general and specific. In re Bextra and Celebrex Mktg. Sales Practices and Prods. Liab. Litig., 524 F. Supp. 2d 1166, 1171-72 (N.D. Cal. 2007) (consumers alleging cardiovascular injury in a products liability suit against drug manufacturer); In re Rezulin Prods. Liab. Litig., 369 F. Supp. 2d 398, 401-02 (S.D.N.Y. 2005) (diabetes patients alleging liver injuries in products liability actions against drug manufacturer). As explained in the Federal Judicial Center's Reference Manual on Scientific Evidence, "General causation is established by demonstrating, often through a review of scientific and medical literature, that exposure to a substance can cause a particular disease . . . . Specific, or individual, causation, however, is established by demonstrating that a given exposure is the cause of an individual's disease . . . ." Mary Sue Henifin et al., Reference Guide on Medical Testimony, in Reference Manual on Scientific Evidence 439, 444 (Fed. Judicial Ctr. 2d ed. 2000) (hereinafter "Reference Guide on Medical Testimony"). Only general causation – whether Neurontin is capable of causing suicide-related events – is at issue in this motion.

Plaintiffs offer the testimony of three experts – Dr.

Michael Trimble,[7] Dr. Stefan Kruszewski,[8] and Dr. Cheryl Blume[9] - to establish general causation. They opine that, by altering the brain chemistry of its users, Neurontin has the biological

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[7] Dr. Michael Trimble is Professor Emeritus of Behavioral Neurology at the Institute of Neurology and Honorary Consultant Physician to the Department of Psychological Medicine at the National Hospital for Neurology and Neurosurgery, both located in London. (Declaration of Professor Michael Trimble, M.D., in Relation to Neurontin Causing Negative Mood and Behavioral Alterations, including Suicidal Behavior, in Treated Patients, at 4-5) (Pls.' Ex. 8) (hereinafter "Trimble Rep.") He holds multiple degrees and has authored or edited several books addressing the interface between neurology and psychiatry, especially in the field of epilepsy and its treatment. (Id.) Dr. Trimble has also published over 120 peer-reviewed papers on similar topics. (Id.) Plaintiffs tout him as the "world's foremost expert with substantial clinical experience regarding antiepileptic drugs' effects on mood and behavior." (Pls.' Mem. in Opp'n 47) (Docket No. 1191.) Moreover, Dr. Trimble has specifically studied and written about Neurontin. In fact, in 1995 and 1996, he was hired by Warner Lambert to investigate the relationship, if any, of Neurontin to psychosis and behavioral disturbances. (See Michael Trimble, Psychosis with Gabapentin (Neurontin), May 20, 1995 (Pls.' Ex. 17); Michael Trimble, Behavioural Disturbance with Gabapentin, Report for Parke, Davis, & Company) (Pls.' Ex. 18.)) Defendants do not challenge his qualifications.

[8] Dr. Stefan Kruszewski is a board certified psychiatrist with a medical degree from Harvard Medical School, specialized training and knowledge in psychopharmacology, and twenty-eight years of clinical practice experience. (See Decl. of Stefan Kruszewski, M.D. ¶¶ 2-9 (Pls.' Ex. 115); Brief Resume, Stefan P. Kruszewski, M.D. (Pls.' Ex. 114.)) His qualifications are discussed in more detail below. See discussion infra Part III.E.

[9] Dr. Cheryl Blume holds a Ph.D. in pharmacology and toxicology from the West Virginia University School of Medicine. Dr. Blume has twenty-five years experience working with pharmaceutical companies to prepare new drug applications and supplemental documents for submission to the FDA. (See Decl. of Cheryl Blume, Ph.D. ¶¶ 1-4 (Pls.' Ex. 102); Curriculum Vitae of Cheryl Blume, Ph.D. (Pls.' Ex. 116.)) Her qualifications are discussed in more detail below. See discussion infra Part III.E.

capacity to cause mood and behavioral changes that predictably result in suicidality. As the Plaintiffs' key witness on the issue of biological plausibility, Dr. Trimble puts forth a three-step explanation for how Neurontin can cause such changes: First, gabapentin (Neurontin) increases the amount of GABA (gamma-aminobutyric acid), a neurotransmitter, in the brain. Second, this increase of GABA leads to a decrease of other neurotransmitters in the brain, like serotonin and norepinephrine.[10] And third, the decrease of serotonin and norepinephrine can prompt behavioral disturbances, depression, and suicidal behavior. Thus, according to Plaintiffs, taking Neurontin can increase a patient's risk of suicidality. All three of Plaintiffs' experts present a variety of scientific evidence, including human and animal studies, case reports, and scientific literature, as support for the position that Neurontin can increase the risk of suicidality in patients.

Defendants challenge the admissibility of Plaintiffs' expert testimony on general causation, asserting that it is insufficiently reliable under Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993), and Federal Rules of Evidence 702 and 703. Defendants contend that Plaintiffs lack scientific evidence demonstrating a statistically significant

[10] Although the increase of GABA is emphasized by Plaintiffs, Dr. Trimble also offers an additional explanation for how gabapentin decreases the release of serotonin and norepinephrine in the brain. See discussion infra III.C.2.c.

association between Neurontin and suicide-related events. According to Defendants, this purported omission is a fatal flaw in Plaintiffs' case. Defendants also attack Plaintiffs' experts' three-step theory of biological plausibility, contending that, as a whole, it lacks widespread acceptance in the scientific community and, more specifically, that particular pieces of the theory are contradicted by current scientific literature. Defendants offered three experts of their own – Dr. Charles Taylor,[11] Dr. Robert Gibbons,[12] and Dr. Anthony Rothschild[13] – to

[11] Dr. Charles Taylor holds a Ph.D. in Neuroscience from the University of California, Berkeley, and has vast experience with the development and study of gabapentin. For over twenty years, Dr. Taylor served as the head preclinical pharmacologist on the gabapentin development team for Defendants (first Parke-Davis and now Pfizer) and authored or co-authored dozens of peer-reviewed papers or book chapters dealing with gabapentin. He retired from his position with Defendants in 2007 and now works as a consultant. (Expert Report: Pharmacology of Gabapentin, Charles P. Taylor, Ph.D., Dec. 20, 2007, at 3-4) (hereinafter "Taylor Rep.").

[12] Robert D. Gibbons, Ph.D. is the Director of the Center for Health Statistics and Professor of Biostatistics and Psychiatry at the University of Illinois at Chicago. He is the recipient of numerous awards, including the Harvard Award for lifetime contributions to the field of Psychiatric Epidemiology and Biostatistics. He has served as a member on the Institute of Medicine Committee on the Prevention of Suicide and on the FDA Scientific Advisory Committee on Suicide and Antidepressants in Children. He has authored over 175 peer-reviewed papers and four books. (Expert Report of Robert D. Gibbons, Ph.D., Neurontin Litigation, May 19, 2008, at 1-2) (Docket No. 1287) (hereinafter "Gibbons May Rep.").

[13] Dr. Anthony Rothschild is a medical doctor with a specialty in psychiatry. A graduate of the University of Pennsylvania School of Medicine, Dr. Rothschild has held various positions at Harvard Medical School and at the University of Massachusetts Medical School, where he is currently a professor.

support their contentions, each of whom submitted a report and testified at the hearing.[14]

C. A Scientific Primer

1. Evidence of Causation in Medicine & the Courtroom

Epidemiology is the field of public health and medicine that studies the incidence, distribution, and etiology of disease in human populations with the purpose of better understanding disease causation. Michael D. Green et al., Reference Guide on Epidemiology, in Reference Manual on Scientific Evidence 333, 335 (Fed. Judicial Ctr., 2d ed. 2000) (hereinafter "Reference Guide on Epidemiology"). "Epidemiology focuses on the question of general causation (i.e., is the agent capable of causing disease?)." Id. at 336.

Dr. Rothschild's research and clinical interests are the neurological bases and pharmacological treatment of depressive disorders, including those carrying a high risk of suicide. Dr. Rothschild serves on the review boards of multiple scientific and medical journals and has published over seventy-five articles in peer-reviewed journals. (Anthony J. Rothschild, M.D., In re: Neurontin General Causation Report, Dec. 19, 2007, at 2-3) (Defs.' Ex. 13) (hereinafter "Rothschild Rep.").

[14] Plaintiffs also submitted multiple declarations by Dr. Sander Greenland, a professor in epidemiology and statistics, for the purpose of interpreting the results of an FDA study and to respond to the assertions of Defendants' expert Dr. Robert Gibbons. (See Decl. of Sander Greenland, March 11, 2008 (Pls.' Ex. 82); Decl. of Sander Greenland, May 2, 2008 (Pls. Sur-Reply Ex. 14); Aff. of Sander Greenland, May 16, 2008 (Docket No. 1352, Ex. 2); Decl. of Sander Greenland, July 22, 2008 (Docket No. 1367, Ex. A.)) Dr. Greenland submitted an expert report to Plaintiffs in October 2007 (Pls.' Ex. 89), but is not designated by Plaintiffs as a general causation expert. Dr. Greenland did not testify at the hearing.

a. *Epidemiological Studies and Statistics*

Epidemiological studies are research studies designed to identify associations between a drug and a disease. These studies generally "identif[y] agents that are associated with an increased risk of disease in groups of individuals, quantif[y] the amount of excess disease that is associated with an agent, and provide[] a profile of the type of individual who is likely to contract a disease after being exposed to an agent." Id. at 335-336. "An association is not equivalent to causation," and so epidemiological studies, on their own, "cannot objectively prove causation." Id. at 336, 374. Instead, an identified association must be evaluated by researchers to determine whether the association is causal. Id. at 374 ("[C]ausation is a judgment for epidemiologists and others interpreting the epidemiological data."). Nevertheless, epidemiological studies are often offered as evidence supporting a theory of general causation in the courtroom. See In re Viagra Prods. Liab. Litig., 572 F. Supp. 2d 1071, 1078 (D. Minn. 2008).

There are many types of epidemiological studies. The "gold standard" for determining the relationship between a drug and a health outcome is a randomized, double-blind, placebo-controlled clinical trial. Reference Guide on Epidemiology, supra, at 338. In such a trial, subjects are assigned randomly to one of two groups: one receives the drug and the other does not, often

receiving a placebo instead. Id. at 338. The study is also "double-blind," meaning that neither the participants nor those conducting the study knows which group is receiving the actual drug and which group is receiving the placebo. Id. These studies are often used to evaluate new drugs or medical treatments, but because ethical constraints preclude exposing human subjects to agents believed to cause adverse effects, these experimental studies cannot be undertaken to investigate a suspicion that a drug increases the risk of suicide. Id. at 338-39; Giles v. Wyeth, 500 F. Supp. 2d 1048, 1058 (S.D. Ill. 2007) ("Suicide presents researchers seeking to study it with both ethical and practical difficulties."). Thus, most epidemiological studies are "observational," not experimental like the studies described above. Observational studies compare subjects already exposed to the drug to those not exposed. Reference Guide on Epidemiology, supra, at 339.

Oftentimes, epidemiological studies lack the statistical power needed for definitive conclusions, either because they are small or the suspected adverse effect is particularly rare. Id. at 380; see, e.g., Giles, 500 F. Supp. 2d at 1058 (noting that, "[a]s a rare event, studying [suicide] for purposes of causation requires a huge number of participants"). The technique of meta-analysis, where study results are pooled "to arrive at a single figure to represent the totality of the studies reviewed," was developed to address such situations. Reference Guide on

Epidemiology, supra, at 380. Meta-analysis "systematiz[es] the time-honored approach of reviewing the literature" and provides a "standardized framework with quantitative methods for estimating risk." Id. Meta-analysis is "most appropriate[ly]" used to pool randomized experimental trials, but "if carefully performed it may also be helpful for observational studies." Id. at 361 n.76.

One statistical approach for expressing an association in epidemiologic research, including meta-analyses, is an odds ratio. Id. at 350. An odds ratio "expresses in quantitative terms the association between exposure to an agent and a disease." Id. An odds ratio uses a null value of 1.0. An odds ratio greater than 1.0 means that there is a positive association, while an odds ratio lower than 1.0 indicates a negative association.

Another method for investigating whether a drug is associated with a particular event is risk difference, or attributable risk.[15] This measure "represents the amount of disease among exposed individuals that can be attributed to the exposure." Id. at 351. Unlike odds ratios, risk differences have a null value of zero. Thus, a risk difference greater than zero suggests a positive association, and a risk difference less

[15] The Reference Guide on Epidemiology speaks of "attributable risk," while experts at the hearing referred to this concept as "risk difference."

than zero suggests a negative association.[16]

The risk difference method is often used in meta-analyses where many of the individual studies (which are all being pooled together in one, larger analysis) do not contain any individuals who developed the investigated side effect.[17] Whereas such studies would have to be excluded from an odds ratio calculation, they can be included in a risk difference calculation.[18]

Regardless of which method – odds ratio or risk difference – is used, a finding of an association is often assessed statistically to determine whether the result likely represents a true association or simply random error. Reference Guide on Epidemiology, supra, at 354. A study found to have "results that are unlikely to be the result of random error" is labelled "statistically significant." Id. Statistical significance, however, does not indicate the strength of an association found in a study. Id. at 359. "A study may be statistically significant but may find only a very weak association;

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[16] For a helpful example describing the calculations undertaken for odds ratio and attributable risk/risk difference analyses, see Reference Guide on Epidemiology, supra, at 350-52.

[17] This scenario is more likely to occur when studying a particularly rare event, such as suicide.

[18] Studies where no individuals experienced the effect must be excluded from an odds ratio calculation because their inclusion would necessitate dividing by zero, which, as perplexed middle school math students come to learn, is impossible. The risk difference's reliance on subtraction, rather than division, enables studies with zero incidences to remain in a meta-analysis. (Hr'g Tr. 310-11, June 20, 2008 (Gibbons.))

conversely, a study with small sample sizes may find a high relative risk but still not be statistically significant." Id. To reach a "more refined assessment of appropriate inferences about the association found in an epidemiologic study," researchers rely on another statistical technique known as a "confidence interval." Id. at 360 (defining a confidence interval as "a range of values calculated from the results of a study, within which the true value is likely to fall"). The width of the confidence interval provides an indication of the precision of the risk figure found in the study. Id. at 389.[19]

b. Non-Epidemiological Evidence

Medical researchers also rely on a variety of non-epidemiological evidence when assessing causation. For example, researchers often examine and analyze case reports, descriptions of a particular patient's clinical history and symptoms. As explained in the Reference Manual on Scientific Evidence: "Case reports lack controls and thus do not provide as much information as controlled epidemiological studies do . . . . Causal attribution based on case studies must be regarded with caution. However, such studies may be carefully considered in light of other information available." Reference Guide on Medical Testimony, supra, at 475.

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[19] For a more detailed explanation of both statistical significance and confidence intervals, see Reference Guide on Epidemiology, supra, at 354-361.

Scientists also look beyond studies on living humans, turning to animals and cell and tissue cultures. Animal studies have the advantage of being able to be conducted as true experiments, with exposure controlled and measured. However, extrapolation from animal studies to humans entails some risks, as physiological differences and dosage differences can complicate comparisons. In re Rezulin Prods. Liab. Litig., 369 F. Supp. 2d at 406-07 (citing Reference Guide on Epidemiology, supra, at 345-46). Experiments on cell and tissue cultures (either human or animal) are often called in vitro studies, as a means of distinguishing them from in vivo studies, meaning on live humans and animals. Id. While in vitro studies are often used, extrapolation from laboratory conditions to live patients can also be problematic. Id.

2. Neurotransmitters[20]

Plaintiffs' theory of how Neurontin causes increased risk of suicide (referred to as a theory of biological plausibility) centers on the impact that Neurontin has on neurotransmitters in the brain. Accordingly, a basic understanding of neurotransmitters is needed to assess Plaintiffs' theory and Defendants' challenges to it.

[20] This discussion reflects this Court's understanding of the basic concepts central to the workings of neurotransmitters and neuronal systems. It is not intended to reflect endorsement of any party's position on a particular issue. The information within this section was gleaned from two textbooks that this Court independently secured.

A neurotransmitter is a natural signaling chemical contained in the body. Communication between cells is essential to the effective functioning of any complex multicellular organism, and the major mode of intercellular communication is the transmission of chemical substances, specifically neurotransmitters. Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy 59 (David E. Golan, et al. eds., 2005).

A nerve cell, or neuron, is connected to another nerve cell, by a specialized junction called a synapse. In a scenario where Nerve Cell A is going to transmit a signal to Nerve Cell B, Nerve Cell A is called the presynaptic cell, and Nerve Cell B is called the postsynaptic cell. Principles of Neural Science 22-23 (Eric R. Kandel et al. eds., 4th ed. 2000). The transmission process begins when an electrical signal, known as an action potential, travels through the presynaptic cell (Nerve Cell A) down to its tip, known as the presynaptic terminal. Id. at 21-23. At the presynaptic terminal are collections of synaptic vesicles, each holding thousands of specific neurotransmitters. Id. at 182. Also at the presynaptic terminal are ion channels, designed for rapid information processing; these channels open and close like gates in response to particular electric or chemical signals. Id. at 105-7, 182-3.

When the signal (action potential) reaches the presynaptic terminal of Nerve Cell A, it causes the channels to open, leading to an influx of calcium ions. This, in turn, triggers the

opening of the synaptic vesicles and the release of the packaged neurotransmitters into the area between the two nerve cells, known as the synaptic cleft. Id. at 183, fig. 10-7. Some of these released neurotransmitters then bind to receptor molecules on the post-synaptic cell (Nerve Cell B), causing that cell's ion channels to open or close, and ultimately creating either an excitatory or inhibitory reaction. Id. at 183-84.

Under Plaintiffs' theory, Neurontin affects several different neurotransmitters in the human brain. First, Plaintiffs contend that Neurontin increases the amount of the neurotransmitter known as GABA in the brain. GABA is the primary inhibitory neurotransmitter in the brain and spinal cord. Golan, supra, at 147; Kandel, supra, at 214. Second, Plaintiffs contend that the increase in GABA leads to a decrease in several monoamine neurotransmitters,[21] namely serotonin, norepinephrine, and dopamine.[22] Serotonin is associated with depression and aggression, while norepinephrine is related to movement and depression. (Trimble Rep. 8); see Principles of Neural Science,

[21] Monoamines are defined as molecules containing one amino group.

[22] Plaintiffs specifically name serotonin as the monoamine neurotransmitter whose reduction prompts behavioral disturbances, depression, and suicidality in some patients taking Neurontin. However, Plaintiffs rely on evidence that all three monoamines (norepinephrine, dopamine, and serotonin) are related to mood and behavior. They also rely on scientific studies indicating that an increase in GABA and/or the ingestion of gabapentin leads to decreases in norepinephrine and dopamine, as well as serotonin.

supra, at 283. Third, an established theory, known as the monoamine theory of depression, states that decreased levels of serotonin and/or norepinephrine neuro-transmission causes depression. (See Trimble Rep. 8) ("Early observations were that drugs which depleted the brain's reserves of monoamines (serotonin, dopamine, and norepinephrine in particular) led to depression."); cf. Golan, supra, at 184. Plaintiffs' experts also present scientific literature that links low levels of serotonin in the brain to suicidal behavior.

3. How Gabapentin Works: The Scientific Debate

Plaintiffs' and Defendants' experts concur that the scientific mechanism by which gabapentin works is not fully understood. (See also Label for Neurontin (Supp. No. 041), April 23, 2009, at 2) (stating that the mechanism by which gabapentin exerts its pain-relief and anticonvulsant actions is "unknown").[23] Developed as an antiepileptic compound, "[g]abapentin was originally conceived to be similar in chemical structure (and therefore in function) to . . . GABA." (Taylor Rep. 5.) As the primary inhibitory neurotransmitter in the brain, GABA has been viewed as a key to designing a therapeutic

[23] As part of their briefing, Plaintiffs submitted the Neurontin Label, Revised 2007. (Pls.' Ex. 11.) A more recent label was recently issued on April 23, 2009. This label has not been submitted to this Court as an exhibit, but is available on the FDA website at http://www.accessdata.fda.gov /scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory.

strategy for epilepsy, a condition precipitated by a lack of inhibition (or an increase in excitation) in some areas of the brain. Thus, many antiepileptic drugs were designed to counteract the over-excitation in an epileptic's brain by increasing the amount of GABA in the brain. (See Hr'g Tr. 52-3, June 19, 2008 (Trimble.)) Such drugs are often referred to as "GABAergic."[24]

Over time, though, researchers began to question whether gabapentin acted in the same way as other GABAergic agents and set out to investigate exactly how the drug worked. Some studies, published in the peer-reviewed literature, have indicated that, rather than acting on GABA-related receptors, gabapentin binds to a subunit of the calcium ion channel located at the edge of a presynaptic nerve cell. (Taylor Rep. 5-6.) Specifically, it is theorized that gabapentin acts at a specific part of the calcium channel known as the alpha-2-delta subunit. (Id.)

Debate over the chemical and pharmacological properties of gabapentin has significant repercussions for this litigation. In advancing their theory of general causation, Plaintiffs characterize gabapentin as a GABAergic drug and rely on studies of other GABAergic drugs which have been shown to lead to

[24] The parties dispute the definition and accepted use of the term "GABAergic." For a discussion of this debate, see infra Part III.B.2.c.

negative effects on mood and behavior. (See, e.g., Trimble Rep. 18) (discussing studies that have "shown that . . . AEDs [antiepileptic drugs] which increase brain GABA lead to negative effects on mood and behavior"). In fact, when hired by Warner Lambert to investigate the relationship between gabapentin and behavioral disturbances in the mid-1990s, Dr. Trimble (now one of Plaintiffs' experts) advised the company that one of the strongest associations with anticonvulsant drugs generally was to depression. (Trimble Rep. 29; see Michael Trimble, Psychosis with Gabapentin (Neurontin), May 20, 1995) (Pls.' Ex. 17.)) And, more recently, the FDA has documented a statistically significant association between GABAergic antiepileptic drugs and an increased risk of suicide.

Defendants, however, contend that the belief that gabapentin is GABAergic (which they admit has been published in peer-reviewed literature) has been "mostly discounted by subsequent research." (Taylor Rep. 6; see id. at 11-16) (listing and discussing studies which suggest that gabapentin has little, if any, GABAergic qualities). Defendants' expert Dr. Taylor insists that "gabapentin is both chemically and pharmacologically distinct" from the GABAergic drugs referenced by Plaintiffs' experts. (Taylor Rep. 4.)

In sum, the parties – and most significantly their two very qualified experts, Dr. Trimble and Dr. Taylor – fundamentally

disagree as to whether gabapentin is properly deemed GABAergic and, significantly, whether Plaintiffs' reliance on comparisons to and extrapolations from studies examining other GABAergic drugs renders their theory of causation unreliable under Daubert.[25]

III. DISCUSSION

A. The Court's Gatekeeping Role

The admission of expert evidence is governed by Federal Rule of Evidence 702, which codified the Supreme Court's holding in Daubert v. Merrell Dow Pharmaceuticals, Inc., 509 U.S. 579 (1993), and its progeny. See United States v. Diaz, 300 F.3d 66, 73 (1st Cir. 2002); see also Fed. R. Evid. 702 advisory committee's note. Rule 702 states:

> If scientific, technical, or other specialized knowledge will assist the trier of fact to understand the evidence or to determine a fact in issue, a witness qualified as an expert by knowledge, skill, experience, training, or education, may testify thereto in the form of an opinion or otherwise, if (1) the testimony is based upon sufficient facts or data, (2) the testimony is the product of reliable principles and methods, and (3) the witness has applied the principles and methods reliably to the facts of the case.

Fed. R. Evid. 702.

The trial court must determine whether the expert's testimony "both rests on a reliable foundation and is relevant to

[25] A more detailed review of both parties' positions in this particular dispute is undertaken in Part III.B.2.c.

the task at hand" and whether the expert is qualified. Daubert, 509 U.S. at 597; Diaz, 300 F.3d at 73 ("[A] proposed expert witness must be sufficiently qualified to assist the trier of fact, and . . . his or her expert testimony must be relevant to the task at hand and rest on a reliable basis . . . ."). An expert's methodology is the "central focus of a Daubert inquiry," but a court "may evaluate the data offered to support an expert's bottom-line opinions to determine if that data provides adequate support to mark the expert's testimony as reliable." Ruiz-Troche v. Pepsi Cola of P.R. Bottling Co., 161 F.3d 77, 81 (1st Cir. 1998); see Bonner v. ISP Techs., Inc., 259 F.3d 924, 929 (8th Cir. 2001) (deeming it clear that "it is the expert witnesses' methodology, rather than their conclusions, that is the primary concern of Rule 702" and stating that a court cannot exclude testimony asserting a "novel" conclusion if the methodology and its application are reliable).

Because "the admissibility of all expert testimony is governed by the principles of Rule 104(a)," the proponents of the expert testimony must establish these matters by a preponderance of the evidence. Fed. R. Evid. 702 advisory committee's note (citing Bourjaily v. United States, 483 U.S. 171 (1987)). "The proponent need not prove to the judge that the expert's testimony is correct, but she must prove by a preponderance of the evidence that the testimony is reliable." Moore v. Ashland Chem., Inc.,

151 F.3d 269, 276 (5th Cir. 1998).

Daubert itself listed four factors which should guide judges in this determination: (1) whether the theory or technique can be and has been tested; (2) whether the technique has been subject to peer review and publication; (3) the technique's known or potential rate of error; (4) the level of the theory's or technique's acceptance within the relevant discipline. United States v. Mooney, 315 F.3d 54, 62 (1st Cir. 2002) (citing Daubert, 509 U.S. at 593-94). "These factors, however, are not definitive or exhaustive, and the trial judge enjoys broad latitude to use other factors to evaluate reliability." Mooney, 315 F.3d at 62 (citing Kumho Tire, 526 U.S. 137, 153 (1999)); see United States v. Vargas, 471 F.3d 255, 261 (1st Cir. 2006) ("The trial court enjoys broad latitude in executing its gate-keeping function; there is no particular procedure it is required to follow."); Hollander v. Sandoz Pharm. Corp., 289 F.3d 1193, 1206 (10th Cir. 2002) (noting that "different courts relying on essentially the same science may reach different results" when evaluating evidence under Daubert).

In Kumho Tire, the Supreme Court was careful to emphasize that the trial judge must exercise her gatekeeping role with respect to all expert evidence, but that how she might exercise that role would necessarily vary depending on the type of testimony at issue. See Kumho Tire, 526 U.S. at 150; United

States v. Frazier, 387 F.3d 1244, 1262 (11th Cir. 2004) ("Exactly how reliability is evaluated may vary from case to case, but what remains constant is the requirement that the trial judge evaluate the reliability of the testimony before allowing its admission at trial."); Amorgianos v. Amtrak, 303 F.3d 256, 266 (2d Cir. 2002) (recognizing that "the Daubert inquiry is fluid and will necessarily vary from case to case").

Under Kumho Tire, the critical inquiry is whether the expert "employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." 526 U.S. at 152; Rider v. Sandoz Pharm. Corp., 295 F.3d 1194, 1197 (11th Cir. 2002). When, for example, "the factual basis of an expert's testimony is called into question, the district court must determine whether the testimony has 'a reliable basis' in light of the knowledge and experience of the relevant discipline." Crowe v. Marchand, 506 F.3d 13, 17 (1st Cir. 2007) (quoting Kumho Tire, 526 U.S. at 148).

The Court's vigilant exercise of this gatekeeper role is critical because of the latitude given to expert witnesses to express their opinions on matters about which they have no firsthand knowledge, and because an expert's testimony may be given substantial weight by the jury due to the expert's background and approach. See Daubert, 509 U.S. at 595; Kumho Tire, 526 U.S. at 148 (noting that experts enjoy "testimonial

latitude unavailable to other witnesses"); United States v. Hines, 55 F. Supp. 2d 62, 64 (D. Mass. 1999) ("[A] certain patina attaches to an expert's testimony unlike any other witness; this is 'science,' a professional's judgment, the jury may think, and give more credence to the testimony than it may deserve.").

The Court must, however, keep in mind the Supreme Court's admonition that, "[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." Daubert, 509 U.S. at 596. If an expert's testimony is within "the range where experts might reasonably differ," the jury, not the trial court, should be the one to "decide among the conflicting views of different experts." Kumho Tire, 526 U.S. at 153. "Only if the expert's opinion is so fundamentally unsupported that it can offer no assistance to the jury must such testimony be excluded." In re Viagra Prods. Liab. Litig., 572 F. Supp. 2d at 1078 (quoting Bonner, 259 F.3d at 929-30. As the First Circuit has stated:

> Daubert does not require that a party who proffers expert testimony carry the burden of proving to the judge that the expert's assessment of the situation is correct. As long as an expert's scientific testimony rests upon "good grounds, based on what is known," Daubert, 509 U.S. at 590 (internal quotation marks omitted), it should be tested by the adversary process – competing expert testimony and active cross-examination – rather than excluded from jurors' scrutiny for fear that they will not grasp its complexities or

> satisfactorily weigh its inadequacies, see id. at 596, 113 S.Ct. 2786. In short, Daubert neither requires nor empowers trial courts to determine which of several competing scientific theories has the best provenance. It demands only that the proponent of the evidence show that the expert's conclusion has been arrived at in a scientifically sound and methodologically reliable fashion.

Ruiz-Troche, 161 F.3d at 85. It is with these principles in mind that the Court assesses Defendants' motion to exclude.

B. Epidemiological Evidence of an Association between Neurontin and Suicide

1. Hiking Bradford Hill

Defendants' first attack on Plaintiffs' evidence of general causation is that Plaintiffs fail to cite to any epidemiological study demonstrating a statistically significant association between Neurontin and suicide-related events. Without solid evidence of such an association, Defendants contend that Plaintiffs' experts' theory of how Neurontin might induce suicide-related events in patients is irrelevant and inadmissible. Referring to the Bradford Hill criteria (discussed further below), Defendants contend that failing to first identify an association between the drug and the negative effect before beginning a causation analysis violates the generally accepted methodology for establishing causation.

Epidemiologic studies, while considered to be "powerful evidence of causation," are not required to prove causation in a

pharmaceutical personal injury case. See, e.g., Rider, 295 F.3d at 1198-99 (citing Eighth, Tenth, and Eleventh Circuit decisions holding that epidemiology is not required to prove causation in a toxic tort case); In re Meridia Prods. Liab. Litig., 328 F. Supp. 2d 791, 800-01 (N.D. Ohio 2004) (surveying the pre- and post-Daubert landscape and concluding that "no court has held that epidemiological evidence is necessary to establish general causation when other methods of proof are available"), aff'd, 447 F.3d 861 (6th Cir. 2006). While an epidemiological study is not per se required, establishing general causation without some "confirmatory" evidence of an association between the drug and the negative effect can be an uphill battle. See Lynch v. Merrell-Nat'l Labs., Inc., 830 F.2d 1190, 1194 (1st Cir. 1987) (holding, in a pre-Daubert opinion, that without "confirmatory epidemiological data," animal studies and extrapolations from studies of analogous drugs cannot establish causation in human beings); see e.g., Rider, 295 F.3d at 1202 (noting that plaintiffs can prove causation via non-epidemiological evidence but holding the evidence in that case to be insufficient).

Defendants are correct in their assertion that an association is the starting point for the Bradford Hill criteria, one accepted approach to establishing causation. See Dunn v. Sandoz Pharms. Corp., 275 F. Supp. 2d 672, 678 (M.D.N.C. 2003) (concluding, in a Daubert inquiry, that an epidemiological study

demonstrating an association is a prerequisite for proper application of Bradford Hill criteria). Developed by Sir Bradford Hill in the 1960s, the criteria are nine factors which researchers often consider when judging whether an observed association is truly causal. The Bradford Hill criteria are:

(1) strength of the association;
(2) consistency;
(3) specificity of the association;
(4) temporality;
(5) dose-response curve;
(6) biological plausibility;
(7) coherence (with other knowledge);
(8) experiment; and
(9) analogy.

A. Bradford Hill, The Environment and Disease: Association or Causation?, 58 Proc. Royal Soc'y Med. 295 (1965) (Defs.' Ex. 16); see Gannon v. United States, 571 F. Supp. 2d 615, 626 (E.D.Pa. 2007) (listing and discussing the nine Bradford Hill factors) Amorgianos v. Nat'l R.R. Passenger Corp., 137 F. Supp. 2d 147, 167-68 (E.D.N.Y. 2001) (same). These factors are viewed as guidelines, and it is acknowledged that each factor need not be fulfilled in order for a researcher to proclaim causation. See A. Bradford Hill, supra, at 11 ("None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non."); Reference Guide on Epidemiology, supra, at 375 (referring to the criteria as "guidelines" and noting that the "drawing of causal

inferences is informed by scientific expertise" as opposed to a strict scientific methodology).[26]

Several courts have recognized the Bradford Hill criteria as a generally accepted "tool for determining whether an epidemiological study establishes causation." Dunn, 275 F. Supp. 2d at 678-79 (citing "the small number" of reported federal and state cases discussing the criteria). Other courts have found the Bradford Hill criteria neither "necessary [n]or helpful." In re Phenylpropanolamine (PPA) Prods. Liab. Litig., 289 F. Supp. 2d 1230, 1243 n.13 (W.D. Wash. 2003). And in the context of a general causation challenge, failure to satisfy the Bradford Hill criteria does not doom admission under Daubert. See, e.g., In re Viagra Prods. Liab. Litig., 572 F. Supp. 2d at 1081 ("The Court agrees that the Bradford Hill criteria are helpful for determining reliability but rejects Pfizer's suggestion that any failure to satisfy those criteria provides independent grounds for granting its Daubert Motion."); Dunn, 275 F. Supp. 2d at 680 (rejecting an expert's Bradford Hill-based testimony because he lacked evidence of an association but separately considering "whether [the plaintiff] can establish general causation independent of the Bradford Hill criteria").

Although courts have not embraced the Bradford Hill criteria

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[26] The Reference Guide provides a modified version of these nine factors. See Reference Guide on Epidemiology, supra, at 375-76.

as a litmus test of general causation, both parties repeatedly refer to the criteria, seemingly agreeing that it is a useful launching point and guide. Accordingly, this Court will begin its inquiry by evaluating Plaintiffs' evidence of an association between Neurontin and suicide-related events, the starting point for an investigation under the criteria.

2. The FDA Study

Plaintiffs trumpet a recent study conducted by the FDA that contains epidemiological data supporting their experts' theories of general causation. In early 2005, the FDA initiated an inquiry into whether the use of antiepileptic drugs ("AEDs") led to an elevated risk of suicidality, defined as suicidal behavior or ideation.

After collecting data from manufacturers, the FDA conducted a meta-analysis, analyzing reports of suicidality from 199 placebo-controlled clinical studies covering eleven different AEDS, including Neurontin (gabapentin). (Statistical Review and Evaluation: AntiEpileptic Drugs and Suicidality, May 23, 2008, at 5) (Docket No. 1332, Ex. A) (hereinafter "Statistical Review"). The analysis included 27,863 patients treated with an AED and 16,029 patients in placebo groups. (Statistical Review at 5.)

On January 31, 2008, the FDA issued an Alert entitled "Information for Healthcare Professionals - Suicidality and Antiepileptic Drugs" ("FDA Alert"), stating: "[P]atients

receiving antiepileptic drugs had approximately twice the risk of suicidal behavior or ideation . . . compared to patients receiving placebo." (FDA Alert 1) (Pls.' Ex. 31.) The Alert reported that the increased risk of suicidal behavior or ideation was "statistically significant," and noted that "[f]our of the patients who were taking one of the antiepileptic drugs committed suicide, whereas none of the patients in the placebo group did." (Id. at 2.) The Alert also reported that patients treated for epilepsy, psychiatric disorders, and other conditions "were all at increased risk for suicidality when compared to placebo," stating that there "did not appear to be a specific demographic subgroup of patients to which the increased risk could be attributed" and that the "results were generally consistent among the eleven drugs." (Id. at 1.) The Alert advised that all patients treated with AEDs should be monitored closely for depression and suicidality and other unusual changes in behavior, explaining that "[s]ymptoms such as anxiety, agitation, hostility, mania and hypomania may be precursors to emerging suicidality." (Id. at 2.)

The Alert cautioned:

> This information reflects FDA's current analysis of available data concerning these drugs. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug products and the emerging safety issue. Nor does it mean that FDA is advising health care professionals to discontinue prescribing these products. FDA

> intends to update this document when additional information or analyses become available.

Id. at 1) (emphasis added); (see FDA Amicus Br. 5 (stating that the Alert "does not constitute a conclusion by FDA that the drugs subject to the Alert actually cause the adverse event," but that, "[o]n the other hand, the disclaimer should not be read to suggest that FDA has concluded that the drugs are *not* causally linked to the adverse events at issue").[27]

In May 2008, the FDA released a "Statistical Review and Evaluation" describing the methodology and analysis it used in evaluating the collected data. The Statistical Review's Executive Summary states: "In conclusion, antiepileptic drugs are associated with increased risk of suicidality relative to placebo in randomized placebo-controlled trials. The effect appears consistent among the group of 11 drugs." (Statistical Review 6.) The review also revealed that the eleven drugs had been divided into three subgroups chosen by the medical officers from the

[27] Recognizing that the FDA meta-analysis, Alert, and subsequent actions were central to issues within the present motion, this Court requested FDA participation in the hearing in this matter. See Letter to David Krawetz, Office of Regulatory Affairs, FDA from the Honorable Patti B. Saris (May 20, 2008) (Docket No. 1301.) The FDA declined to provide testimony at the hearing, but submitted an amicus brief addressing the agency's purpose and policy in issuing alerts, the status of its consideration of the relationship between suicidality and AEDs, and its position that testimony by an FDA employee would be inappropriate. See Mem. of the United States Food and Drug Admin. as Amicus Curiae (hereinafter "FDA Amicus Br.") (Docket No. 1351.)

FDA's Division of Neurology. Gabapentin, along with four other drugs, was placed within the GABAergic and GABAmimetic drug group. (Id. at 13.) When tested by drug group, the GABAergic/GABAmimetic group demonstrated a statistically significant association with increased risk of suicidal behavior or ideation. (Id. at 32, fig. 7.) Finally, the statistical review revealed that, in addition to the primary analysis, the FDA also conducted three sensitivity analyses to examine the robustness of its primary analytical method.

On July 10, 2008, the FDA held a Joint Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee ("PCNS") and the Psychopharmacologic Drug Advisory Committee ("PDAC").[28] The meeting was open to the public and offered "interested persons" the opportunity to "present data, information, or views, orally or in writing." Meeting Notice, 73 Fed. Reg. 32588 (June 9, 2008). The Committee heard presentations from representatives of two drug manufacturers of AEDs contained within the FDA's study, including Defendant Pfizer, and additional statements from an FDA Safety Reviewer. Discussing the significance and methodology of the FDA's meta-

[28] There were twenty-one voting members present at the meeting, almost all of whom hold either a Ph.D or an M.D. and are professors or researchers at a major university, medical center, or the National Institute of Health. The lone member not associated with such an institution is a medical doctor and is on the committee as a "Consumer Representative." (See Meeting Roster, Docket No. 1365, Ex. D.)

analysis, Dr. Russell Katz, the FDA Director of the Division of Neurology Products, stated: "We're unequivocally comfortable with . . . saying that this establishes causality." (Transcript of the Joint Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee and the Psychopharmacologic Drug Advisory Committee, July 10, 2008, at 90) (Docket No. 1365, Ex. G) (hereinafter "FDA Hr'g Tr.").[29] Emphasizing that the agency had applied its regular methodology for determining causality, Dr. Katz then repeated his position that the FDA is "quite comfortable with saying there is causality." (FDA Hr'g Tr. 90.)

At the close of the meeting, the Committee members voted on four questions. First, the Committee, with twenty in favor and one abstention, voted to affirm the FDA's overall finding of an increase in suicidality for the eleven AEDs analyzed. Second, the Committee, with eighteen in favor and three against, affirmed the FDA's conclusion that the finding of increased suicidality should apply to each of the eleven drugs in the analyses. Third, the Committee, with fifteen in favor, five against, and one abstention, affirmed the FDA's conclusion that the finding should apply to all currently approved chronically administered AEDs, including drugs beyond the eleven included in the analysis. Finally, the Committee rejected, by a vote of fourteen to four

[29] This Court received multiple copies of the transcript, with different pagination. All citations to the FDA Advisory Committee Meeting Transcript are to the transcript filed as Exhibit G to Docket No. 1365.

with three abstentions, a proposal to place a "black box" warning (the most serious available) on the labels for all AEDs. However, the Committee did approve, by a vote of seventeen to four, a proposed labeling change for AED medication guides.

On December 16, 2008, the FDA announced that it had completed its analysis and, based on the outcome of its review, is requiring all manufacturers of antiepileptic/anticonvulsant drugs to include a warning in their labeling and to inform patients of the risks of suicidal thoughts and actions. (See Updated FDA Alert, Dec. 16, 2008 (Docket No. 1600, Ex. A.)) The FDA stated that the general consistency of results among drugs with "varying mechanisms of action and across a range of indications suggests that the risk applies to all antiepileptic drugs used for any indication," id., but did not articulate a theory as to how such drugs increased the risk of suicidal thoughts and actions in patients. (Press Release, FDA News, FDA Requires Warnings about Risk of Suicidal Thoughts and Behavior for Antiepileptic Medications, Dec. 16, 2008) (stating that the biological reasons for the increased risk are "unknown") (Docket No. 1600, Ex. D.)

Neurontin's revised label now contains an extensive seven paragraph warning, detailing the results of the meta-analysis and stating, inter alia:

Suicidal Behavior and Ideation

> Antiepileptic drugs, including Neurontin, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior . . . . The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed.

Neurontin Label, April 23, 2009, at 10. The label also contains a section discussing information that should be provided to patients:

> Patients, their caregivers, and families should be counseled that AEDs, including Neurontin, may increase the risk of suicidal thoughts and behavior and should be advised of the need to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts about self-harm . . . . Patients should be advised that Neurontin may cause dizziness, somnolence and other signs of CNS depression.

Neurontin Label, April 23, 2009, at 13.

It is widely recognized that, when evaluating pharmaceutical drugs, the FDA often uses a different standard than a court does to evaluate evidence of causation in a products liability action. Entrusted with the responsibility of protecting the public from dangerous drugs, the FDA regularly relies on a risk-utility analysis, balancing the possible harm against the beneficial uses of a drug. Understandably, the agency may choose to "err on the side of caution," Rider, 295 F.3d at 1201, and take regulatory

action such as revising a product label or removing a drug from the marketplace "upon a lesser showing of harm to the public than the preponderance-of-the-evidence or more-like-than-not standard used to assess tort liability." McClain v. Metabolife Int'l, Inc., 401 F.3d 1233, 1250 (11th Cir. 2005) (quoting Glastetter v. Novartis Pharm. Corp., 252 F.3d 986, 991 (8th Cir. 2001)). In fact, FDA regulations provide that the agency can issue an Alert or warning label even before causation is established, (Hr'g Tr. 128-9, June 19, 2008 (Blume)), and the agency has, in a recent guidance document, stated that it has "begun taking a more comprehensive approach to making information on potential drug risks available to the public earlier." (FDA Amicus Br. 2) (quoting Guidance: Drug Safety Information - FDA's Communication to the Public (March 2007)).[30] This earlier disclosure allows "healthcare professionals and patients [to] . . . consider the information when making decisions about medical treatment" even when there may be "uncertainties in the data." Id. at 3. As such, the decision by the FDA to require warnings on a drug label, without more, does not suffice to establish causation.

Plaintiffs argue persuasively that even if this Court does not consider the FDA study as definitive proof of general causation, the study nevertheless qualifies as powerful epidemiological evidence establishing an association between

[30] The March 2007 Guidance document is available at http://www.fda.gov/cder/guidance/7477.fnl.pdf.

Neurontin and suicidality. Whether the FDA meta-analysis is properly termed an epidemiological study is an area of dispute between the parties. Defendants' expert Dr. Gibbons acknowledged that some would call it an epidemiological study, but disagreed with that characterization. (Hr'g Tr. 299-300, June 20, 2008.) He takes the position that, because the meta-analysis combined the results of many small clinical trials, it does not bear the hallmark characteristic of an epidemiological study, which, he says, typically involves very large populations. (Id.) On the other hand, Plaintiffs' experts Blume and Trimble – who are not epidemiologists or biostatisticians but work regularly with such data – both testified that the study qualified as an epidemiological study. (Hr'g Tr. 57, June 19, 2008 (Trimble); Hr'g Tr. 170, 174, June 20, 2008 (Blume.)) Moreover, the Reference Guide on Epidemiology suggests that a meta-analysis can itself be deemed an epidemiological study. See Reference Guide on Epidemiology, supra, at 380. For reasons discussed below, the Court finds that the FDA study is an epidemiological study that may be considered on the question of whether the Plaintiffs have produced evidence of an association between Neurontin and suicidality (the starting point for a causal inquiry under Bradford Hill).

a. Dr. Gibbons' Critique

Defendants strenuously argue that the FDA study contains

methodological flaws, which produce a misleading picture of the data. In their view, the data actually suggest that only two of the eleven drugs – neither of which is Neurontin – are associated with increased suicidality. Thus, Defendants maintain that any claim that the FDA Alert demonstrates an association between Neurontin and suicidality is erroneous.

Defendants' expert Dr. Robert Gibbons critiques the FDA study, stating that it fell prey to what he describes as a serious, but not uncommon, problem with meta-analyses: that a subset of the studies can "drive the overall results, making it appear as if there's an overall effect that's consistent." (Hr'g Tr. 380-81, July 23, 2008.) Here, Dr. Gibbons points the finger at two of the eleven drugs: "My postmortem on the FDA Alert is that the entire analysis was driven by lamotrigine and topiramate. If those two drugs were not a part of FDA's analysis, there would be no FDA Alert on anticonvulsants." The issue raised by Dr. Gibbons is often referred to as "trial heterogeneity." (Hr'g Tr. 320-21, June 20, 2008.) Gibbons highlights the fact that sixty-one percent of all of the suicidality events (thoughts and behaviors) observed in the entire meta-analysis came from the lamotrigine and topiramate studies, even though these two drugs account for only thirty-eight percent of the total data. (Supp. Expert Rep. of Robert D. Gibbons, July 11, 2008 at 2) (Docket No. 1363, Ex. A.)

(hereinafter "Gibbons July Rep."). Moreover, he points out that these two drugs were the only ones in the analysis which demonstrated a statistically significant increased risk in both the primary and secondary sensitivity analyses. (Gibbons July Rep. 2; Statistical Review at 24, fig. 2; 26, fig. 4.) While several other drugs, including Neurontin, demonstrated a positive association with suicidality events, these associations were not statistically significant. As further evidence for his position, Dr. Gibbons offered his own analysis of the data, in which he separated lamotrigine and topirimate from the other nine AEDs in the meta-analysis. While lamotrigine and topirimate together demonstrated a statistically significant association, the other nine AEDs in combination did not. (Gibbons July Rep. ¶ 3.)

The "revelation" that these two drugs are driving the entire study, according to Dr. Gibbons, undercuts two FDA conclusions upon which Plaintiffs rely: (1) that the results were consistent among the eleven drugs, and (2) the FDA's finding of a statistically significant association within the GABAergic or GABAmimetic drug subgroup, a group which included both topiramate and Neurontin.

With respect to the GABAergic/GABA mimetic subgroup, Gibbons again insists that topiramate was the driving force behind the statistically significant finding; without topiramate, the remaining four drugs in the GABAergic subgroup together have an

incidence rate of suicide events "virtually identical" to patients treated with placebo and thus producing no signal, much less one with statistical significance. (Gibbons ¶ 4; Hr'g Tr. 320, June 20, 2008 (Gibbons.)) Gibbons also points out that topiramate, which was found to increase the risk of suicidality in patients approximately two-and-a-half times, was the only one of the five drugs which, when analyzed independently, produced a statistically significant association. Grouping these five drugs together was therefore, according to Gibbons, empirically inappropriate:

> [T]hese five drugs are showing very different results. Topiramate is going one way, and all of the other drugs are going the other way . . . [F]rom an empirical basis, based solely on the numbers . . . it's inappropriate to apply a statistical method that assumes that all five of these drugs have a common risk . . . . You cannot come up with a reliable conclusion about the pooled risk when you have that level of heterogeneity.

(Hr'g Tr. 321-22, June 20, 2008.)

Having laid out his argument as to why the FDA's overall finding of an increased risk of suicidality and its particular finding of an increased risk within the GABAergic subgroup are flawed, Dr. Gibbons next turns his eye to the gabapentin-specific data. In the FDA's primary analysis, gabapentin yielded an odds ratio of 1.57, indicating a positive association between the drug and suicidal behavior or ideation. However, Gibbons emphasizes

that the perceived association had an extremely wide confidence interval (.12 to 47.66) and was not statistically significant; thus the possibility that the association occurred by chance cannot be ruled out. (FDA Statistical Review 24, fig. 2.)

Dr. Gibbons also attacks the FDA study for employing an odds ratio methodology, in which the FDA excluded all studies where no suicidality events occurred ("zero event" studies) from its primary meta-analysis. See discussion supra, at Part II.C.1.a. Gibbons maintains that because only three of the forty-nine studies on Neurontin submitted to the FDA by Defendants included qualifying incidents of suicidality (two incidents of suicidal ideation in Neurontin-treated patients and one in a patient receiving a placebo), this approach translated to the exclusion of the vast majority of the gabapentin data from the initial FDA analysis, arguably skewing the gabapentin-specific analysis.

The FDA, however, did not ignore this limitation. As part of its sensitivity analysis, the FDA applied a risk difference analysis (an alternative method which does not require the exclusion of zero event studies), see discussion supra, Part II.C.1.a, to all of the data submitted for each of the eleven drugs. Here, the gabapentin-specific data yielded a 0.28 risk difference, indicating a positive association. Gibbons emphasizes that it is a small association that was deemed not statistically significant. Gibbons characterized this finding as

evidence indicating that "for gabapentin, [there was] no increased risk of suicidality observed." (Gibbons July Rep. ¶ 5.)

In sum, Dr. Gibbons concludes that, in light of what he deems serious methodological and analytical flaws, the FDA's statement that "the results were generally consistent among all the different drug products" is not supported by the data. (Gibbons July Rep. ¶ 6.) Gibbons contends that the agency selected "really bad methods" for examining "whether or not the effects they were seeing applied to all of the drugs." (Hr'g Tr. 401-02, July 23, 2008.) For Gibbons, the bottom line is that, in his view, neither the FDA study nor any evidence put forth by Plaintiffs demonstrates that gabapentin itself is associated with suicidality or supports a conclusion of a causal link between gabapentin and suicidality. (Gibbons May Rep. 16.)

b. Does the FDA Study Withstand Dr. Gibbons' Critique?

Dr. Gibbons has presented a powerful critique of the FDA's statistical analysis and its conclusion that the increased risk of suicidality detected in its meta-analysis is "consistent among the group of 11 drugs." (FDA Statistical Review 6.) However, on balance, Dr. Gibbons' criticism of the FDA's statistical methods and conclusions – particularly its conclusion of consistency in effect among the eleven drugs – affects the weight that should be given to the study, not its admissibility. First, the underlying

data for the FDA's meta-analysis were placebo-controlled, clinical studies, the "gold standard" for epidemiological evidence.[31] And, as the Reference Manual on Scientific Evidence explains, pooling such evidence is the "most appropriate" application of the meta-analysis method. Reference Guide on Epidemiology, supra, at 380.

Moreover, the FDA has continued to stand by its statistical methods and conclusions even after considering the very concerns raised by Dr. Gibbons. As detailed in the Statistical Review, the FDA conducted several sensitivity analyses "to examine the robustness" of the results generated by the study's primary analysis. (FDA Statistical Review 43.) In fact, two of the sensitivity analyses addressed the key concerns raised by Gibbons. One sensitivity analysis specifically examined the question of trial heterogeneity, the primary critique raised by Dr. Gibbons. The FDA applied two separate tests to evaluate whether all eleven drugs were properly grouped together in the primary analysis or whether the drugs' "treatment effects" were too heterogenous – or different from each other – to justify such pooling. While the first test was inconclusive, the second model produced a result that convinced the FDA that "trial heterogeneity was not a major concern" and that, therefore, it was appropriate to group all eleven drugs together in the meta-

[31] The studies, though, were not necessarily double-blinded.

analysis. (FDA Statistical Review 27.)

At the Advisory Committee meeting three statisticians expressed general approval of the FDA's technical approach to the study's analyses. Then, the entire group was asked whether they agreed with the Agency's overall finding of an increase in suicidality for the eleven AEDs analyzed. The Committee voted yes, with a tally of twenty to zero (with one abstention). The second question was whether "the Committee agree[s] with the Agency's conclusion that [the] finding of increased suicidality should apply to all, or each, of the drugs included in the analysis, despite the observation that the odds ratio for two of the drugs was below one." (FDA Hr'g Tr. 94.) Again, the Committee signaled its agreement with the FDA, with eighteen members voting "yes" and three voting "no."

Perhaps most persuasive is that these votes each came after the Committee members had heard Dr. Christopher Wohlberg, on behalf of Pfizer, argue that it was improper to pool the eleven drugs together and that the effects were not consistent across all eleven drugs. (Id. at 37.) In fact, Dr. Wohlberg articulated the very point Dr. Gibbons emphasized in his testimony: that topiramate and lamotrigine were driving the results of the study. (Id. at 38.) Yet, even after this testimony, this blue ribbon Committee voted to affirm the FDA's methods and conclusion of consistency among the eleven drugs.

In addition, Plaintiffs' expert Dr. Sander Greenland,[32] a statistician and epidemiologist, rebuts many of Dr. Gibbons' arguments. Greenland concludes that "[t]he FDA Analysis was in all respects conducted properly and followed the current best standards of practice." (Decl. of Sander Greenland, July 22, 2008, at 2.) Dr. Greenland also declared that he "concur[s] with the . . . vote of the . . . Advisory Committee, agreeing with the FDA finding of increase in suicidality for the drugs examined." (Id. at 11.) Thus, while reputable experts may disagree as to the strength of the study's methodology and its findings, this Court considers the FDA study to be reliable and potent evidence supporting an association between Neurontin and depression or suicidality.

c. Drug-specific Evidence

Still, the FDA study is not a silver bullet for Plaintiffs. Standing alone, the Neurontin-specific data produced a positive association, but not a statistically significant one. Defendants

[32] Dr. Greenland is Professor of Epidemiology at the UCLA School of Public Health and Professor of Statistics at the UCLA College of Letters and Science. His co-authored textbook Modern Epidemiology is used in numerous schools of public health and medicine and has been cited in peer-reviewed journals and the Federal Judiciary Center's Reference Manual on Scientific Evidence. Dr. Greenland has authored hundreds of peer-reviewed articles and has served in leadership positions on both the Society for Epidemiologic Research and the American Statistical Association, both the largest societies in the world in their fields. (See Expert Report of Sander Greenland, Oct. 19, 2007, at 3-6) (Pls.' Ex. 89.)

insist that the FDA's findings of association (overall and within the GABAergic subgroup) are not an adequate substitute for a drug-specific statistically significant finding.

Statistical significance is one of the factors the Court should examine when determining whether a drug can cause an adverse event. See Daubert, 509 U.S. at 594 ("[I]n the case of a particular scientific technique, the court ordinarily should consider the known or potential rate of error."). Drug-specific statistical significance, though, is not always required where it is not reasonably attainable. In Kennedy v. Collagen Corporation, 161 F.3d 1226, 1228 (9th Cir. 1998), the Ninth Circuit reversed the trial court's exclusion of general causation testimony because the trial court had improperly "focused on the lack of specific studies" proving the particular collagen product at issue caused the disease. The Kennedy court emphasized that epidemiological studies linking the collagen product to the disease "would be almost impossible to perform." Id. at 1229; see also Giles, 500 F. Supp. 2d at 1058-61 (allowing plaintiff to present her theory of general causation and discussing the difficulties of studying suicide and suicidality for purposes of causation).

As discussed above, because suicide is a rare event, large numbers of subjects are needed to produce informative results. (Id.) Plaintiffs' experts point out that the gabapentin studies

submitted to the FDA are simply too small and contain too few high-risk psychiatric patients to produce an informative finding as to whether gabapentin itself is associated with an increased risk of suicide. Dr. Trimble explains that the placebo-controlled studies used in the meta-analysis are designed for therapeutic, not adverse effect, inquiries. Here, because Neurontin was developed and initially approved as an antiseizure medication, the pool did not include many psychiatric patients. This potential bias was further compounded by the purposeful exclusion of many psychiatric patients based on previous studies indicating that GABAergic antiseizure medications may have serious behavioral impacts. As a result, in Trimble's view, the gabapentin-specific data did not include enough psychiatric, or high risk, patients necessary to establish a link between Neurontin and suicide-related side effects.[33] (Hr'g Tr. 74-76, June 19, 2008.)

From a statistical viewpoint, Dr. Greenland adds his conclusion that, because (or at least partially because) the gabapentin data was dominated by low risk patients, the data was so "underpowered" that there was "over a 90% chance that a doubling of risk by gabapentin would go *undetected* by the

[33] Dr. Trimble also points out that a number of the gabapentin trials included in the data submitted to the FDA involved people who only received a single tablet, a dose that would not likely prompt suicidal behavior. (Hr'g Tr. 77, June 19, 2008.)

gabapentin trials." (Decl. of Sander Greenland, July 22, 2008, at 8) (emphasis in original). This, in Greenland's view, makes it "all the more remarkable that the gabapentin trials were able to see as much of a risk increase as they did (a risk ratio of 1.49)." Id.

Accordingly, in these circumstances, the fact that there is no statistically significant information about Neurontin alone is not dispositive, particularly since there is statistically significant information about the class of drugs and other indicia of reliability. Cf. In re Viagra Prods. Liab. Litig., 572 F. Supp. 2d at 1081 (holding, in a pharmaceutical drug products liability multi-district litigation, that an expert's report was reliable even though there was no statistically significant epidemiological data because it was based upon studies that were peer-reviewed, published, contained known rates of error and resulted from generally accepted experience or research data); In re PPA Prods. Liab. Litig., 289 F. Supp. 2d at 1241.

In pressing their theory that gabapentin increases the risk of suicide, Plaintiffs seek to extrapolate not only from the FDA's overall finding that "antiepileptic drugs are associated with increased risk of suicidality" (Statistical Review 6), but also from the finding of a statistically significant association within the GABAergic or GABAmimetic drug subgroup, which included

Neurontin and four other drugs. (Statistical Review 32, Fig. 7.)

Extrapolating from drugs within the same class is permissible, so long as there is there is scientific evidence supporting the analogy. See Kennedy, 161 F.3d at 1230 (deeming admissible an expert's testimony that was based on analogous reasoning). Other courts have wrestled with the question of whether an analogy between drugs in the same class is reliable enough to support a plaintiff's theory of general causation. See McClain, 401 F.3d at 1246 (rejecting an expert's attempt to analogize because he had "failed to show that the . . . analogy [was] valid or that the differences in chemical structure between [the two drugs] make no difference"); Glastetter, 252 F.3d at 990 (noting that the "generic assumption" that a drug behaves like others in its class "carries little scientific value" because "[e]ven minor deviations in molecular structure can radically change a particular substance's properties and propensities"); Hollander v. Sandoz Pharm. Corp., 95 F. Supp. 2d 1230, 1238 (W.D. Okla. 2000) (rejecting plaintiffs' attempt to extrapolate from evidence linking other drugs in the same class to hypertension because they failed to demonstrate that the drugs had "sufficiently similar physiological effects to warrant comparison" and "failed to refute" evidence of chemical and biological diversity within the drug class), aff'd, 289 F.3d 1193, 1207 (10th Cir. 2002) (noting that several courts have

agreed with the district court's conclusion and citing cases).

Defendants challenge the position that gabapentin is sufficiently similar to these other drugs – both those in the subgroup and the class of AEDs as a whole – to support extrapolation.

Aside from their statistical arguments, Defendants argue that the FDA was wrong in its evaluation of the physiologic properties of gabapentin and that, therefore, the FDA's conclusion of similarity is faulty. Defendants, via Dr. Taylor, argue that "gabapentin is both chemically and pharmacologically distinct" from other GABAergic drugs and that drawing analogies between gabapentin and these drugs is "not a reliable or generally accepted methodology." (Taylor Aff. ¶ 13, March 12, 2008) (provided at hearing). Citing to peer-reviewed and published articles, Dr. Taylor asserts that current reviews of gabapentin's mechanism of action have undermined the FDA's classification of gabapentin as GABAergic. (Taylor Rep. 5, 10-16.) In essence, Defendants boldly invite the Court to proclaim the FDA and its panel of blue-ribbon experts dead wrong.

However, in contrast to the cases cited above, Plaintiffs' experts present convincing scientific evidence as to why the analogy between Neurontin and other GABAergic antiepileptic drugs makes sense and is sufficiently reliable. Plaintiffs' expert Dr. Trimble states, "It has been shown experimentally in the peer-

reviewed scientific literature that gabapentin significantly and reliably increases the quantity of [central nervous system] GABA in the human brain." (Trimble Rep. 25.) Trimble then cites and discusses two peer-reviewed studies measuring changes in GABA levels after administration of gabapentin in humans in vivo- both of which he characterizes as supporting the proposition that gabapentin is GABAergic.[34] Dr. Trimble also cites to an in vitro study of gabapentin-treated human neocortical tissue which reported an increase in GABA, confirming the results of the two studies performed on live patients.[35] (Id.) Moreover, citing published literature[36] and internal Pfizer documents,[37]

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[34] See O.A.C. Petroff, et al., Gabapentin raises human brain GABA within thirty minutes, 8 Proc. Int'l Soc. Mag. Reson. Med. 14, 14 (2000) (Pls.' Ex. 39); R. Kuzniecky, et al., Modulation of cerebral GABA by topiramate, lamotrigine, and gabapentin in healthy adults, 58 Neurology 368, 368 (2002) (finding that a single dose of gabapentin increased brain GABA within six hours and stating that, over the course of 4 weeks, "significant elevations in GABA were observed").

[35] See Laura D. Errante, et al., Gabapentin and vigabatrin increase GABA in the human neocortical slice, 49 Epilepsy Research 203-210 (2002)) (Pls.' Ex. 129.)

[36] Dr. Trimble cites two pieces of literature for this proposition. (See Trimble Rep. 23-4 (citing H.S. White, Mechanism of action of newer anticonvulsants, 64 J. of Clinical Psychiatry (Supplement 8) 5-8 (2003); E. Perucca, The New Anticonvulsants *in* Seizures, Affective Disorders and Anticonvulsant Drugs 1-18 (Trimble et al, eds., 2002)). In addition, Plaintiffs cite to a 2006 article, stating that "Trimble's hypothesis of a link between psychiatric complications and GABA-ergic mechanisms of AED [antiepileptic drugs] was extended by [another researcher]" and places gabapentin within the category of GABA-ergic AEDs. See Bettina Schmitz, Effects of Antiepileptic Drugs on Mood and Behavior, 47 Epilepsia (Supplement 2) 28-33 (2006) (Pls.' Slides from Closing Argument,

Plaintiffs' experts demonstrate that gabapentin has been presented by Pfizer as a GABAergic drug and generally regarded as such in the scientific community (particularly the epilepsy research community). (See, e.g., Trimble Rep. 23-24); Hr'g Tr. 92, June 19, 2008 (Trimble) (stating that when study results first indicated that gabapentin was GABAergic, the "news was heralded with great enthusiasm" by Defendants.)) Most notably, Dr. Trimble cites to a 2003 company email which not only references multiple studies finding that gabapentin causes an increase in GABA in the human brain, but also acknowledges that the increases in GABA "might contribute to . . . adverse events in humans." (E-mail from Douglas Feltner to Charles Taylor, Elizabeth Carofalo, Chiara DePaolis, Brian Corrigan, Timothy Wang, and Douglas Feltner (Oct. 14, 2003)) (Pls.' Ex. 51.) In sum, Dr. Trimble describes the conclusion that Neurontin is a GABAergic drug as "secure," stating, "[a]t no time has there been in the scientific literature a specific rejection of the

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July 23, 2008) (Docket No. 1373, Ex. E at 31.)

[37] For example, Plaintiffs submitted a Pfizer-created chart titled, "Mechanisms of action of anticonvulsants," which groups gabapentin with four other drugs, including vigabatrin, under the heading, "Enhancement of GABAergic neurotransmission." This document, originally produced internally by Defendants, was published in 1994. (Pls.' Sur-Reply Ex. 1.) Also, in his report, Dr. Trimble cites a post-2000 communication document of Defendants which states, "Gabapentin is considered a GABA-modulationg [sic] agent, and affects brain GABA through multiple mechanisms. Gabapentin has been shown to enhance GABA synthesis, increase whole-brain GABA, and promotes presynaptic GABA release through nonvesicular mechanisms." (Trimble Rep. 23.)

GABAergic properties of neurontin." (Trimble Rep. 23, 41.)

Significantly, Defendants do not dispute that gabapentin has been shown to prompt an increase in whole-tissue brain concentrations of GABA, but assert that these findings do not establish that gabapentin is "GABAergic" because they do not prove either that gabapentin impacts GABA within specific GABA neurons or synapses or actually affects the function of the GABA neurotransmitters. This argument highlights yet another dispute among experts. Under defense expert Dr. Taylor's definition, for a drug to be deemed GABAergic, it must act on specific GABA receptors or GABA neurons and effect the release or function of GABA. (Taylor Rep. 9, 14-15.) On the other hand, Plaintiffs' expert Dr. Trimble states that, among epilepsy specialists and biological psychiatrists, GABAergic is defined as a drug that increases either the amount or the effect of GABA.[38] (Hr'g Tr. 43-44, June 19, 2008.) Even more variations of the definition exist, as Dr. Taylor readily admitted that there is no generally accepted definition in the field. (Hr'g Tr. 347, June 20, 2008) ("[I]f you asked ten different people, you might get at least three different answers.").

Putting this definitional dispute aside, it is undisputed

[38] At the hearing, Dr. Trimble asserted that additional studies demonstrate that the increase in GABA caused by gabapentin has a functional effect (increasing inhibition) outside of individual cells. (Hr'g Tr. 86, 88-89, June 19, 2008 (Trimble.))

that Defendants designed gabapentin as a GABAergic drug. (See Taylor Rep. 5, 10.) Although Defendants maintain that the "gabapentin as GABAergic" literature cited by Plaintiffs is outdated, the FDA, by keeping gabapentin in the GABAergic subgroup, still adheres to the traditional view, rejecting the Pfizer position. In addition, as discussed above, Plaintiffs' experts cite to several articles published in recent years identifying gabapentin as GABAergic, and even Dr. Taylor has acknowledged that several post-2000 studies have reported findings indicating that gabapentin has a functional impact on GABA. (See Taylor Rep. 12 (acknowledging that "some investigators have reported a functional action of gabapentin . . . in vitro . . . that is similar to those of known GABA(B) agonists"); Taylor Rep. 13 (acknowledging several studies demonstrating an effect of gabapentin on release of GABA in vitro and a 2001 study showing that gabapentin increased the number of GABA transport proteins present at the cell membrane").)[39] Finally, Dr. Trimble firmly stated that he, and many of his colleagues in the epilepsy field, still view gabapentin as a GABAergic agent. (Hr'g Tr. 91-92, June 19, 2008.) Under Daubert, Plaintiffs do not have to demonstrate that all scientists believe that gabapentin is GABAergic, but simply that

[39] Dr. Taylor maintains, however, that these studies have not been shown to be applicable to an analysis of gabapentin's effect on humans in clinical settings. (Taylor Rep. 13)

their experts' "testimony rests upon 'good grounds, based on what is known.'" Ruiz-Troche, 161 F.3d at 85 (quoting Daubert, 509 U.S. at 590). While Pfizer has presented scientific evidence to support its view that Neurontin may differ from traditional GABAergic antiepileptic drugs, Plaintiffs – via their own scientific evidence and the methodology employed by the FDA – have emonstrated that gabapentin is sufficiently similar to these drugs to render pooling and extrapolation "scientifically sound and methodologically reliable." Id. at 85.

In sum, this Court views the FDA findings as reliable evidence of an association between Neurontin and an increased risk of suicide.

3. The Collins & McFarland Study

Plaintiffs' experts also rely on a study and peer-reviewed article, authored by Jon C. Collins and Bentson H. McFarland, as evidence of an association between Neurontin and suicide.[40] The study compared rates of completed suicide and suicide attempts among patients with bipolar disorder taking four different drugs. (Collins & McFarland Study at 2.) The gabapentin group demonstrated the "highest rate" of completed suicides (3.5 per thousand person-years) among all four drugs. Id. at 4. When

[40] See Jon C. Collins and Bentson H. McFarland, Divalproex, lithium, and suicide among Medicaid patients with bipolar disorder, J. Affect. Disord. (2007) (e-publication, forthcoming in print), available at doi:10.1016/j.jad.2007.07.014) (Defs.' Ex. 18) (hereinafter "Collins & McFarland Study").

compared to lithium (which exhibited the lowest rate), gabapentin was found to have a statistically significant greater risk of suicide completion (2.6 times) and a greater, but not statistically significant, risk of suicide attempt (1.6 times).

The experts have varied interpretations of this study. Dr. Trimble characterized the study as one "of great importance," emphasizing that it "showed a significant over-representation of patients on gabapentin for suicide deaths." (Trimple Rep. 19.) But Dr. Greenland, Plaintiffs' expert statistician, cautions that the study has limitations: the study's findings cannot indicate whether gabapentin is only "riskier" than lithium (which is considered by some researchers to help prevent suicidal behavior) or whether it actually is associated with an increased risk of suicide in general patient populations, bipolar or otherwise. (Expert Report of Sander Greenland, Oct. 19, 2007, at 3-6.) Defendants' experts argue that the study's data demonstrates that Neurontin is actually protective of suicide – the exact opposite of Plaintiffs' characterization of the findings.

While the Collins & McFarland study is consistent with the FDA's findings, Defendants have the better argument that it does not provide independent proof of an association or causation.

C. Plaintiffs' Theory of Biological Plausibility

Having established an association between Neurontin and an increased risk of suicide, Plaintiffs have satisfied the

prerequisite for a causation analysis using the Bradford Hill methodology. See Dunn, 275 F. Supp. 2d at 678. In addition to lengthy debate over the existence, strength, and specificity of the association, most of the hearing focused on the question of biological plausibility, a key factor in the Bradford Hill analysis. Plaintiffs' experts put forward a three-step theory for how Neurontin can cause mood and behavioral changes that predictably result in suicidality. Defendants contend that this theory of biological plausibility fails to satisfy Daubert's requirements.

1. Does Gabapentin Increase the Amount of GABA in the Brain?

The first step in Plaintiffs' theory of biological plausibility is that gabapentin increases the amount of GABA in the brain. Given the admission by Defendants that gabapentin increases the amount of GABA in the whole brain and the general acceptance – by the FDA and relevant scientific specialties of the medical community – that gabapentin is a GABAergic drug, this first step in Plaintiffs' theory, as discussed above, has "a reliable basis" on which to stand. Crowe, 506 F.3d at 17 (quoting Kumho Tire, 526 U.S. at 148); see discussion supra Parts II.C.3., III.B.2.c.

2. Does Gabapentin Lead to a Decrease in Monoamines?

In arguing biological plausibility, Plaintiffs emphasize their claim that gabapentin is GABAergic or increases the amount

of GABA in the brain. However, Plaintiffs' expert Dr. Trimble acknowledges that the mechanism by which gabapentin acts in precipitating suicidal behavior could either stem from gabapentin's "GABAergic effect and/or the results of its action at the alpha-2-delta protein." (Trimble Rep. at 6.) Thus a more precise articulation of the second step of Plaintiffs' causation theory is that, regardless of the biological mechanism by which gabapentin acts (i.e., whether by its GABAergic effect or its binding at the alpha-2-delta protein), gabapentin decreases several monoamine neurotransmitters – namely, serotonin, norepinephrine,[41] and dopamine. Plaintiffs generally focus on serotonin, identifying it as the primary monoamine neurotransmitter whose reduction prompts behavioral disturbances, depression, and suicidality in particular patients taking Neurontin.

a. In vitro studies

It is generally accepted and Defendants do not dispute that the presence of GABA in the nuclei where serotonin originates (the raphe nuclei) reduces the rate of serotonin release. This finding was repeatedly demonstrated, via animal models, by researchers in the 1980s and was published in multiple peer-reviewed articles. (Trimble Rep. 9-10; Hr'g Tr. 48-9 (Dr.

[41] Norepinephrine is synonymous with noradrenaline and is part of the noradrenergic system.

Trimble describing the studies and Defendants stating that they do not dispute the findings); see Pls.' Exs. 42, 45-47.) While these experiments involved several GABAergic antiepileptic drugs, none studied gabapentin itself.[42]

Thus, Plaintiffs' experts present additional, gabapentin-specific evidence which they contend demonstrates that gabapentin leads to a decrease in the release of monamine transmitters (i.e. serotonin, norepinephrine, and dopamine). Specifically, Plaintiffs rely on animal studies, each published and peer-reviewed, that have reported that gabapentin inhibits the release of dopamine, norepinephrine, and serotonin.[43] Defendants acknowledge these studies; in fact, the findings were discussed in a July 2001 internal Pfizer research report titled, "Summary of Preclinical Pharmacological Studies With Gabapentin . . . In

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[42] While Defendants do not dispute that an increase in GABA in the raphe nuclei, if it occurs, can lead to a decrease in serotonin, they assert that Plaintiffs have not produced any studies establishing that gabapentin causes such an increase of GABA within the raphe nuclei. Here again, Defendants contend that the spectroscopy studies relied on by Plaintiffs' experts have limited applicability because they do not distinguish between an increase in intracellular and extracellular GABA. (See Taylor Rep. 14; Hr'g Tr. 49-50, June 19, 2008.)

[43] See, e.g., Schlicker, et al., Gabapentin decreases monoamine release without affecting acetylcholine release in the brain, 35 Drug Res. 1347 (1985) (Pls.' Ex. 43); Dooley et al., Stimulus-dependent modulation of [3H]norepinephrine release from rat neocortical slices by gabapentin and pregabalin, 296 J Pharmacol. Exp. Ther. 10896 (2000) (provided at hearing); Fink et al., Inhibition of neuronal CA(2+) influx by gabapentin and subsequent reduction of neurotransmitter release from rat neocortical slices, 130 Br. J. Pharmacol. 900-906 (2000).

Vitro and in Laboratory Animals." (See Pfizer Global Research and Development Research Report, Summary of Preclinical Pharmacological Studies with Gabapentin . . . In Vitro and in Laboratory Animals, July 19, 2001, at 39-40) (provided at hearing). This confidential report was authored by Defendants' expert Dr. Taylor and summarizes twenty years of studies examining gabapentin's pharmacological effects, including in vitro studies designed to examine the effects of gabapentin on the release of monoamine transmitters. (Id. at 7.) As summarized by Dr. Taylor in the report, several animal studies have demonstrated that gabapentin decreases monoamine neurotransmitter release in vitro. (Id. at 41.) Specifically, Dr. Taylor reported that gabapentin caused a reduction of norepinephrine of twenty to forty percent and a significant reduction in the release of dopamine as well. (Id. at 39-40) (acknowledging that "it is possible that these effects of gabapentin on monoamine neurotransmitter release contribute to their effects in anxiety and other mood disorders").

Nevertheless, Defendants contend that these studies are insufficient to establish that Neurontin reduces levels of serotonin and other monoamines in humans. First, Dr. Taylor criticizes Plaintiffs' experts for relying on in vitro (laboratory) studies, stating that extrapolating from a laboratory setting to predict outcomes in living beings is not a

generally accepted methodology or practice. (Taylor Aff. ¶ 25; Taylor Rep. 19) (stating that it is "widely understood that in vitro studies of neurotransmitter overflow in . . . brain tissue samples do not model or precisely replicate all aspects governing monoamine release in vivo").[44]

Second, Dr. Taylor maintains that extrapolation from in vitro animal studies is particularly inappropriate in this case because the rat brain slices in the in vitro studies relied on by Plaintiffs were subjected to artificial electrical stimulation. According to Dr. Taylor, such a "synchronized massive stimulation" would never occur in intact animals or humans during normal behavior or disease. (Taylor Aff. ¶ 24.) Therefore, in Taylor's view, these studies are ultimately irrelevant to an inquiry into the effects of the drug in a human or whole animal. (Hr'g Tr. 446-47, July 23, 2008.) In sum, Defendants do not dispute that, once the rat brain tissue was stimulated, gabapentin reduced the release of monoamines, but they dismiss the results recorded during this stimulated, or "hyperexcited," state as beside-the-point and theoretical. Instead, they contend that these same in vitro studies actually demonstrate that gabapentin has little or no effect on the release of monaomines. (Taylor Rep. 24) ("Although gabapentin reduced the

[44] One problem with this method, according to Taylor, is that the brain slices used in in vitro experiments do not contain any of the regions of the brainstem that control monoamine release in a normal intact organism. (Taylor Rep. 19-20.)

artificially 'stimulated' release of monoamines by 20 to 40%, it had no effect on the 'basal' release of monoamines (without application of either potassium or electrical shocks) . . . . gabapentin has little or no effect on the release of monoamines in the absence of severe (abnormally strong) and synchronized presynaptic stimulation in whole tissues.").[45]

Notably, however, while Dr. Taylor competently points out the limitations of these in vitro studies, he concedes that the very methods he critiques have "been used by numerous research teams for more than 30 years as a model to study various physiological and pharmacological aspects of neurotransmitter release" at monoamine-containing neurons. (Taylor Rep. 18.)

b. In vivo studies

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[45] To illustrate this point at the hearing, Dr. Taylor used what he characterized as "one representative figure" from one of the several in vitro studies to illustrate his point. (Hr'g Tr. 445, July 23, 2008); see Dooley DJ, Donovan CM, Pugsley TA, Stimulus-dependent modulation of [3H]norepinephrine release from rat neocortical slices by gabapentin and pregabalin, 296 J Pharmacol. Exp. Ther. 1086, 1089, fig. 3 (2000) (provided at hearing.)) The figure shows two time course line graphs; one graph tracked the amount of norepinephrine in the control group while the other tracked the amount of norepinephrine in the gabapentin group. It was only in the stimulated time period that the two lines diverged significantly, with the gabapentin-treated line showing markedly less norepinephrine than present in the control group. In the segments before and after the stimulation, the two lines were nearly identical, indicating that gabapentin did not have much effect on the amount of monoamines when the tissue was unstimulated. (Hr'g Tr. 445-47, 449-50, July 23, 2008.) This outcome has, according to Taylor, been "consistently found" in other in vitro experiments. (Taylor Rep. 24) (citing five studies).

Dr. Taylor contends that, in addition to in vitro studies, studies using "intact animals" (i.e., in vivo studies) and other methods are required to determine the effects a drug has on the release of monoamine neurotransmitters in humans. (Taylor Aff. ¶ 25; Taylor Rep. 19-20.) He cites two "whole animal" studies which he contends "reinforce the view that gabapentin does not change the release of monoamine neurotransmitters in animals behaving normally in vivo."[46] (Taylor Rep. 25.) Yet he places the greatest emphasis on two human studies examining gabapentin's effect on monoamine neurotransmitters. These two peer-reviewed studies, both conducted by Dr. Elinor Ben-Menachem and published in the 1990s, are the only such studies involving human subjects. The first study, published in 1992, was a short-term experiment with only five human subjects.[47] It evaluated the influence of one dose of gabapentin on the release of dopamine and serotonin

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[46] See Taylor Aff. ¶ 26 (citing Pugsley et al., Reduction of 3, 4-Diaminopyridine-Induced Biogenic Amine Synthesis and Release in Rat Brain by Gabapentin, 137 Psychopharmacology 74 (1998) (finding, in Taylor's words, that "even high dosages of gabapentin did not alter turnover of serotonin, noradrenaline, or dopamine" except when artificial stimulation preceded gabapentin administration); N. Andrews et al., Effect of Gabapentin-Like Compounds on Development and Maintenance of Morphine-Induced Conditioned Place Preferences, 157 Psychopharmacology 381 (2001) (showing no effect of gabapentin on dopamine release in living rats)).

[47] See Elinor Ben-Menachem, et al., Selected CSF biochemistry and gabapentin concentrations in the CSF and plasma in patients with partial seizures after a single oral dose of gabapentin, 11 Epilepsy Research 45-49 (1992) ("1992 Ben-Menachem study") (Defs.' Ex.. 54.)

over the course of three days. The study found a "tendency for HVA[48] [dopamine] and 5-HIAA[49] [serotonin] to increase after 24 and 72 h[ours] post dose." (1992 Ben-Menachem study 48.)

The second study, published in 1995, was of longer duration and greater size.[50] In this double-blind placebo-controlled experiment, thirty-six human patients received either 900 mg of gabapetin per day, 1200 mg of gabapentin per day, or a placebo for three months. Measurements of monoamines in the participants' cerebrospinal fluid were taken both before and after the three-month treatment period. The results indicated that there were no significant differences between the "before" and "after" levels of both dopamine [HVA] and serotonin [5-HIAA] in the patients treated with gabapentin. (1995 Ben-Menachem study 234) ("There was no influence of GBP [gabapentin] on HVA [dopamine] or 5-HIAA [serotonin] in the CSF."). Defendants argue that this "no effect" finding in the 1995 study undercuts Plaintiffs' theory. They also characterize the 1992 study as

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[48] "HVA" is the abbreviation for homovanillic acid, which is the principal breakdown product of the monoamine neurotransmitter dopamine. (Hr'g Tr. 67, June 19, 2008 (Trimble.))

[49] "5-HIAA" is the abbreviation for 5 hydroxyindoleacetic acid, which is the principal breakdown product of serotonin. (Hr'g Tr. 67, June 19, 2008 (Trimble.))

[50] See Elinor Ben-Menachem, et al., Seizure Frequency and CSF parameters in a double-blind placebo controlled trial of gabapentin in patients with intractable complex partial seizures, 21 Epilepsy Research 231-36 (1995) (hereinafter "1995 Ben-Menachem study") (Pls.' Ex. 78; Defs.' Ex. 53; Defs.' Hr'g Ex. 2.)

having demonstrated the opposite (a serotonin increase) of what Plaintiffs theorize (a serotonin decrease).

Plaintiffs' expert Dr. Trimble refutes the Defendants' characterization of the 1992 study findings, stating that, given the short-term nature of the 1992 study, the finding of an increase in serotonin is "entirely what you would expect," even if the ultimate impact of the drug is to reduce serotonin in the patient. (Hr'g Tr. 64, June 19, 2008.) Trimble explains that, when a patient is given a drug whose effect is to block the receptors of a particular neurotransmitter, the brain's immediate response is to produce a "huge outflow" of that neurotransmitter. (Id.) This initial outflow, however, ultimately results in the depletion of the stores of that neurotransmitter; if the drug treatment is continued over a longer time period, a decrease in the "turnover"[51] will occur.[52] (Hr'g Tr. 64-65, June 19, 2008.)

Turning to the 1995 Ben-Menachem study, Trimble emphasizes that, particularly at the 1200 mg dosage level, the experiment

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[51] For purposes of this discussion, a decrease in the "turnover" of a monoamine (e.g., serotonin) means a decrease in the amount of that monomaine. (Hr'g Tr. 65, June 19, 2008 (Trimble).)

[52] This effect is verified, Trimble says, by two other Ben-Menachem studies: a 1989 Ben-Menachem study examining the effect of vigabatrin (a GABAergic antiepileptic drug associated with depression) on the release of serotonin and the 1995 Ben-Menachem study discussed above. Ben-Menachemn's vigabatrin experiment, as explained by Trimble, demonstrated that "while a single dose [of vigabatrin] increased serotonin turnover, chronic administration resulted in decreases of serotonin turnover." (Trimble Rep. 27.)

revealed a slight decrease of serotonin after three months of gabapentin treatment. (Hr'g Tr. 68, June 19, 2008.) (See 1995 Ben-Menachem Study 233, fig. 5.) Trimble acknowledges that there is no indication that the decrease is statistically significant, but states that a visual comparison of the bars reflecting levels of serotonin before and after three months treatment at 1200 mg dosage "reflect[s] a decrease." (Hr'g Tr. 68, June 19, 2008.) This decrease is all the more noticeable when compared with the placebo results, which indicate an increase in serotonin turnover. (Id.) Thus, in Trimble's view, the 1995 Ben-Menachem study, while not conclusive, "supports the view that in the human brain, with chronic gabapentin treatment, you get down regulation of activity of this key neurotransmitter for mood regulation; namely, serotonin." (Hr'g Tr. 69, June 19, 2008.) Thus, the experts dispute the proper interpretation of the results of the 1995 Ben-Menachem study.

Finally, Defendants take the position that it is a decrease – not an increase – in GABA levels in the brain that can lead to depressive effects. Defendants rely on The Textbook of Psychopharmacology which states that, in replicated studies, GABA concentrations in depressed patients have been shown to be "significantly lower" than those in nondepressed control subjects and that "GABA concentration was inversely correlated with

severity of depression."[53] (Alan Schatzerg & Charles Nemeroff, eds., Textbook of Psychopharmacology, 736 (3d ed. 2002) (Defs.' Slides for Taylor Direct Examination, at 3) (Docket No. 1375, Ex. 2.)

c. Kumho Wrestling

While Defendants have demonstrated that there is a robust debate in the scientific community on whether gabapentin decreases the release of monoamines, Plaintiffs have put forth reliable scientific evidence from a highly qualified expert, Dr. Trimble, who relies in part on peer-reviewed animal studies documenting such a decrease. It is true that Dr. Trimble cannot explain with a reasonable degree of scientific certainty how gabapentin might prompt a decrease in monoamines. Instead, he relies on an "either/or" explanation, contending that Neurontin either prompts an increase of GABA which causes a reduction in the rate of serotonin release or, by binding to the subunit of the alpha-2-delta protein, somehow triggers a decrease in

[53] Defendants take this argument one step further, contending that an increase in GABA may actually have anti-depressive effects. Citing several studies, Defendants point out that increased amounts of whole brain GABA has been shown to occur with electroconvulsive therapy and selective serotonin reuptake inhibitors ("SSRIs"), both known treatments for depression and suicidality. In addition, Defendants point to one study finding increased amounts of GABA after participation in yoga exercises. Dr. Trimble, however, rejects the Defendants' characterization of the studies' findings as overreaching and misleading.

monoamine production.[54] (See, e.g., Trimble Rep. 6 (stating that when gabapentin is given to a patient with a mood disorder [or a history of mood disorders], "the GABAergic effect and/or the results of its action at the alpha-2-delta protein precipitates suicidal behavior") (emphasis added); Hr'g Tr. 231, June 20, 2008 (Kruszewski) (stating that, regardless of which mechanism theory you ascribe to, the "end result" is a "reduction in the release of monoamine neurotransmitters").

Significantly, Pfizer has, in both internal and external communications over the course of many years, repeatedly acknowledged that gabapentin has been shown to reduce the release of monomaine neurotransmitters. (See Trimble Rep. 36 ("The findings that gabapentin decreases the release of key monoamines in the depression/impulsivity/suicide narrative is also constantly referred to in the company documents, and investigative brochures.")). As representative examples, Defendants' 1993 Product Monograph states, "Neurontin slightly reduces the release of monoamine neurotransmitters in vitro."

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[54] To support the first explanation, Dr. Trimble relies on the uncontested in vitro animal studies demonstrating that, by causing an increase of GABA in serotonin-related nuclei, other GABAergic antiepileptic drugs reduced the rate of serotonin release. For the latter explanation, Dr. Trimble states that there "are peer-reviewed papers showing that gabapentin produces this effect by its action on calcium channels." (Trimble Rep. 10-11) (citing Fink et al., Inhibition of neuronal Ca(2+) influx by Gabapentin and subsequent reduction of neurotransmitter release from rat neorcortical slices, 130 British J. of Pharmacology 900-906 (2002)).

(Pls.' Ex. 25.), and a 2001 internal Project Operating plan reads: "Gabapentin has been known to reduce monoamine neurotransmitter release for many years." (Pls.' Sur-Reply, Ex. 5.)

There is therefore, in the peer reviewed scientific literature and Pfizer's own literature, "'good grounds'" to support testimony that gabapentin causes a decrease in monoamines like serotonin. Ruiz-Troche, 161 F.3d at 85 (quoting Daubert, 509 U.S. at 590). That two key experts, Dr. Taylor (who has spent his professional life researching Neurontin for Pfizer) and Dr. Trimble (who was once hired by Pfizer to research Neurontin and is eminent in his field) vigorously disagree on the interpretation of the existing literature makes clear that Plaintiff's theory falls squarely within "the range where experts might reasonably differ" and is thus proper fodder for a jury. Kumho Tire, 526 U.S. at 153; see Ruiz-Troche, 161 F.3d at 85 ("Daubert neither requires nor empowers trial courts to determine which of several competing scientific theories has the best provenance.").

3. Does a Decrease in Monoamines Lead to Depression and Suicidality?

The third step in Plaintiffs' theory is that a decrease in serotonin and/or norepinephrine created by gabapentin can prompt behavioral disturbances, depression, and suicide. As stated by

Plaintiffs' expert Dr. Kruszewski, "a depletion of monoamines, particularly serotonin and norepinephrine, or an inhibition of those monoamines' functional activities, [creates] a significantly increased risk of mood and behavioral disturbances." (Stefan Kruszewski, Gabapentin: Mechanism of Mood-altering Action, at 11) (hereinafter "Kruszewski Rep.") (Pls.' Ex. 28.) These disturbances ultimately "result[] in inter alia, dysphoria, sadness, depression, abnormal thinking, depersonalization, irritability, agitation, aggression, suicidal behavior and completed suicides." (Id.) Dr. Trimble articulates the same proposition in his report: "The decrease in the functional activity of serotonin and norepinephrine . . . results clinically in depression, anxiety, panic, irritable mood, dysphoria, anger, agitation, hostility, [and] impulsivity," ultimately precipitating suicidal behavior in certain individuals. (Trimble Rep. 6.) According to Dr. Trimble, there are two ways in which Neurontin can cause suicidal behavior. First, the link between the drug and suicidality can be "direct," with the drug causing the precipitation of aggressive emotions. Or, the link can be "indirect," through the onset of depression caused by the drug. (Trimble Rep. 15.)

a. Serotonin and Mood

The premise that the decrease of serotonin and other monoamines in the brain is deleterious to mood including

depression and aggression is supported in the literature[55] and not controversial, as even Defendants' experts and employees acknowledge.[56] Moreover, the acceptance of a connection between serotonin and depression is illustrated by the pervasive use of Selective Serotonin Reuptake Inhibitors ("SSRIs") as an antidepressant medication. SSRIs bind to the serotonin transporter in the brain and block the "reuptake" of serotonin,

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[55] Plaintiffs characterize this finding as "[o]ne of the most established findings in the whole of biological psychiatry," (Pls.' Mem. in Opp'n 20), and cite several publications, including two pharmacology textbooks for support. See, e.g., The Handbook of Psychopharmacology Trials: An Overview of Scientific, Political, and Ethical Concerns 299 (Marc Hertzman and Douglas E. Feltner, eds. 1997) ("Enhanced levels of aggressive behavior follow serotonin depletion in animals.") (Pls.' Ex. 59); Cooper, et. al., The Biochemical Basis of Neuropharmacology, 290-93 (5th ed. 1986) (stating that "[t]here is mounting evidence for impaired serotonergic function in major depressive illness and suicidal behavior" and discussing the development of antidepressant drugs which act on the serotonin system) (Pls.' Ex. 63.) In addition, Plaintiffs' expert Dr. Trimble states that the serotonin system has been linked to the regulation of affect and that "[e]arly observations were that drugs which depleted the brain's reserves of monoamines (serotonin, dopamine and norepinephrine in particular) led to depression." (Trimble Rep. 13.)

[56] In their depositions, two defense experts – Dr. Rothschild and Dr. Gerard Sanacora – testified that serotonin is related to mood and behavior. (See Rothschild Dep. 12:18-23, Jan. 15, 2008 (stating that both serotonin and norepinephrine are "related to mood and behavior") (Pls.' Ex. 67); Sanacora Dep. 79: 8-9, Jan. 8, 2008 ("I would say changes in serotonergic system has been associated with differences in mood.") (Pls.' Ex. 61)). In addition, Pfizer employee and a member of the Neurontin worldwide team, Dr. Leslie Tive testified at her deposition that a reduction in monoamines has been associated with depression and that "[a]n increase or decrease of serotonin in the brain can be associated with depression." (Tive Dep. 300: 11-24, July 19, 2008) (Pls.' Ex. 66).

thereby increasing the amount of serotonin in the human brain. (See Kruszewski Rep. 12 ("That decreased serotonergic and noradrenergic activity is casually [sic] related to depression and suicide forms the basis of previous and present-day antidepressant treatment."); see also Blanchard v. Eli Lilly & Co., 207 F. Supp. 2d 308, 311 (D. Vt. 2002) ("There is medical and scientific evidence that SSRIs . . . are effective in treating major depressive disorders. This is because depression is associated with serotonin depletion in many people, and SSRIs are thought to increase the activity of the neurotransmitter serotonin in the brain.")).

b. Serotonin and Suicide

An association between low levels of serotonin in the brain and suicide is also well documented, appearing in peer-reviewed literature spanning several decades. (See Trimble Rep. 12 (stating that the relationship between suicide and low serotonin release is "one of the most replicated findings in the whole of biological psychiatry"); Kruszewski Rep. 11 (describing the association between reduced central levels of serotonin and depression and suicide as "long established and supported by the referenced and published literature")). Taken together, two generations of studies have established that "at least part of the pathology related to suicidal behavior is reduced serotonin turnover or serotonergic neuron activity." Guide to Suicide

Assessment and Intervention 102 (Douglas G. Jacobs, ed., 1999) (Pls.' Ex. 70) (hereinafter "Guide to Suicide Assessment"). The first generation of studies reported modest reduction in levels serotonin in the brainstem of suicide victims, while the next set of studies connected low levels of serotonin in cerebrospinal fluid ("CSF") to suicidal behavior.[57] (Id. at 102) (concluding that "[f]uture suicide and attempted suicide are associated with low CSF 5-HIAA").

A host of more recent articles and textbooks confirms that the association between low serotonin levels and depression and suicide remains generally accepted in the field. In fact, a recent peer-reviewed article declared that the "ample evidence of an association" between serotonin neurotransmission and suicidal behavior, achieved via many different research methods, "suggest[s] a causal interpretation of this association." Kees van Heeringen, 48 The Neurobiology of Suicide and Suicidality, Can. J. Psychiatry 292, 296 (June 2003) (provided at hearing).[58] While defense expert Dr. Sanacora disagrees with the causation

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[57] Plaintiffs submitted articles and textbook excerpts describing both generations of studies.

[58] Also in 2003, an article heralded the results of a recent study involving serotonin receptors as "add[ing] ammunition to the case that serotonin abnormalities underlie suicidal behavior." See Joan Arehart-Treichel, Data Back Relationship Between Serotonin Binding, Suicide Attempts, Psychiatric News, June 20, 2003, at 26 (noting that postmortem evidence has indicated that serotonin abnormalities in the brain underlie suicidal thoughts and behavior) (Pls.' Ex. 64.)

label, even he admits that there is a "fairly large literature base showing abnormal measures of serotonin associated with suicide victims."[59] (Sanacora Dep. 87:8-88:25, Jan. 18, 2008) (Pls.' Ex. 66.)

These studies also report an association between lowered serotonin levels and aggression, which can manifest in suicidal acts.[60] Also significant is that the connection between reduced serotonergic activity and suicide is not limited to a particular psychiatric diagnosis. In the studies examining the brainstem of suicide victims, the degree of reduction in serotonin was similar in depressed patients, schizophrenics, personality disorders, and alcoholics. As stated in the Guide to Suicide Assessment and Intervention, "[t]his is a critical point because it indicates that the reduction in serotonin activity is related to suicide independent of psychiatric diagnosis." Guide to Suicide Assessment, supra, at 100; see van Heeringen, supra, at 298. (stating that the relationship between serotenergic dysfunction and suicidal behaviors is "not confined to depressive disorders .

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[59] Dr. Sanacora is a psychiatrist and neuropsycho-pharmacologist who produced an expert report for Defendants. (See Defs.' Ex. 52.) He did not testify at the Daubert hearing.

[60] See, e.g., Plaicidi, et. al., Aggressivity, Suicide Attempts, and Depression: Relationship to Cerebrospinal Fluid Monoamine Matabolite Levels, Soc' of Biological Psychiatry 783, 789 (2001) (stating that six out of seven studies examined found an inverse relationship between CSF 5-HIAA and aggression and that "low serotonin functioning appears to be implicated mostly in impulsive aggression").

. . . [as it] also appears to be involved in the development of suicidal behaviour in the context of other disorders, such as schizophrenia, substance abuse, and bipolar disorder"); (Trimble Rep. 13 ("Importantly the studies with 5-HIAA link alteration of the levels of this metabolite of serotonin to impulsivity and aggression, rather than any DSM IV diagnosis . . . . [T]he findings do not apply only to people with personality disorders, but also across a spectrum of psychiatric diagnoses.")).

Thus the conclusion that alterations in monoamine neurotransmitters, including serotonin, can impact mood and behavior and is associated with depression, aggression, and suicide, has been published extensively in peer reviewed literature and is widely accepted in the scientific and medical community.[61] Accordingly, the third step of Plaintiffs' theory passes muster, at least with respect to serotonin depletion.[62]

D. Additional Evidence: Adverse Event Data

Plaintiffs offer examples of adverse events experienced in patients as further support for their general causation theory.

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[61] In addition to scientific literature, Plaintiffs also cite to multiple prescribing physicians who state that depletion of serotonin or other monoamines can cause depression or other mood disturbances.

[62] While the record does not support the proposition that a decrease in norepinephrine alone is associated with suicide, there is sufficient support for the notion that, in general, monoamines such as norepinephrine are associated with changes in mood and behavior.

Courts may, and often do, rely on other lines of causation evidence such as adverse event data. See, e.g., In re PPA Prods. Liab. Litig., 289 F. Supp. 2d at 1242 (finding "the sheer volume of case reports, case series, and spontaneous reports" to be "significant" and instructive in its reliability assessment). To be sure, Plaintiffs and Defendants agree that adverse event reports ("AERs") – whether published in safety databases or the medical literature – have significant limitations. See ; In re Baycol Prods. Liab. Litig., 532 F. Supp. 2d 1029, 1039-40 (D. Minn. 2007) (noting that the "FDA has published certain caveats" as to the proper use of adverse event reports and citing multiple court opinions addressing the reliability of AERs); McClain, 401 F.3d at 1253-4 ("Because they are anecdotal, 'case studies lack controls and thus do not provide as much information as controlled epidemiological studies do . . . . Causal attribution based on case studies must be regarded with caution.'") (quoting Reference Guide on Medical Testimony, supra, at 475).

Plaintiffs also use a subset of adverse event data, known as dechallenge and rechallenge events. A positive dechallenge event refers to a situation where a patient's adverse event partially or completely disappears after the patient stops taking the drug. If the patient later resumes taking the drug, and one or more of the adverse events reoccur, the event is known as a positive rechallenge. See Glastetter, 252 F.3d at 990. As other courts

have noted, dechallenge and rechallenge data "is substantially more valuable than run-of-the-mill case reports because a patient's reactions are measured against his own prior reactions." Id.; see Giles, 500 F. Supp. 2d at 1051 n.7. More generally, adverse event data can contribute to an evaluation under the Bradford Hill criteria, where temporal relationship is one of the many factors considered.

1. Adverse Events in Pre- and Post-Approval Clinical Trials

Plaintiffs' experts cite to data submitted by Pfizer to the FDA as part of its New Drug Application for Neurontin in 1992 as additional evidence supporting their theory of general causation. The data, summarized in an FDA report, documents adverse events reported in all controlled and uncontrolled clinical trials conducted by Pfizer through June 2002, reflecting a total of 2,048 patients exposed to gabapentin.[63] (See Division of Neuropharmacological Drug Products Combined Medical-Statistical Review, Oct. 13, 1993, at 77) (Pls.' Ex. 5) (hereinafter "1993 Med.-Stat. Review"). In the total exposed population of patients in the New Drug Application, seventy-eight, or 5.3 percent, of the reported adverse events were of depression, including nineteen instances where the patient had no prior history of

[63] The 2048 exposed patients came from three separate submissions: The New Drug Application (submitted Jan. 31, 1992); a First Safety Update (submitted May 29, 1992); and a Second Safety Update (submitted Nov. 11, 1992). (1993 Med.-Stat. Review 74.)

depression, twenty-two instances where the patient required treatment for his or her depression, and nine instances where the patient had to withdraw from the study due to the depression. (1993 Med.-Stat. Review 109, 114.) The adverse event data was also broken down by severity, with each of the events categorized as "serious" or "non-serious." As stipulated in FDA regulations, a "serious" adverse event is defined as "immediately life threatening, permanently disabling, or requiring hospitalization . . ., overdose, . . . or other events deemed of medical concern." (Id. at 102) (citing 21 C.F.R. § 312.32(a)). Seventy-eight "serious" adverse events were identified (from the 2048 patients exposed), including seven reports of depression (each involving suicidal ideation), six of drug overdoses, and two suicide attempts. (Id. at 102, 109.) Six of the seventy-eight "serious" incidents, including both suicide attempts, were deemed by the clinical investigator to be "possibly or probably" related to gabapentin. (Id. at 107.)

After detailing all of the data, the 1993 FDA Review describes gabapentin's safety profile as "generally good," but notes that "several important concerns" remain. (Id. at 116.) The report identified five "serious events," including depression, which could "limit the drug's widespread usefulness," and stated, "depression, while it may be not an infrequent occurrence in the epileptic population, may become worse and

require intervention or lead to suicide, as it has resulted in some suicidal attempts." (Id. at 117) (listing "clinically important depression" as one of "five groups of important adverse events that have not yet been fully characterized").

Plaintiffs' expert Dr. Blume also draw upon adverse event data from the clinical studies of gabapentin conducted after its epilepsy-based approval in 1993 (particularly studies from the 1994-1996 time period).[64] Having reviewed these studies, Dr. Blume emphasized that a greater percentage of patients in the gabapentin-treated group experienced serious psychobiologic adverse events than those in the placebo-treated group (17.3 percent gabapentin patients versus 13.8 percent placebo patients). She also reported that, of those patients who had to withdraw because of the severity of a psychobiologic side effect, nearly twice as many were from the gabapentin-treatment group as compared to the placebo group (26 percent versus 14 percent). (Blume Rep. ¶ 96.) At the hearing, Dr. Blume highlighted these calculations, explaining that they are the type of summary data that the FDA requires drug companies to compile for safety

[64] Dr. Blume cites to clinical pharmacology studies, monotherapy studies, and the STEPS trial, a "large, multicenter" trial designed to "evaluate the safety and tolerability of gabapentin on the patient's quality of life and the relationship between gabapentin dose and plasma concentrations." (Expert Report of Dr. Cheryl Blume, Oct. 22, 2007, at ¶ 72) (hereinafter "Blume Rep.") (Pls.' Ex. 4.) Dr. Blume also reviews data from studies examining gabapentin's effectiveness in treating bipolar disorder, social phobia, panic disorder, and diabetic peripheral neuropathy. (Blume Rep. ¶ 82.)

assessments of their products. (Hr'g Tr. 123, June 19, 2008).

2. Dechallenge / Rechallenge Events

According to Dr. Blume, observations of dechallenge and/or rechallenge events are significant and, in some instances, can be deemed a safety "signal."[65] (Blume Rep. ¶¶ 55-56.) A positive dechallenge "can represent evidence that the drug under study was responsible for or associated with the adverse event"; the case is even stronger, therefore, when a positive rechallenge is present. See U.S. Dept. of Heath and Human Services, Food and Drug Administration, Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiolgic Assessment 4 (March 2005) ("It is possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge . . . ."") (Pls.' Hr'g Ex. 3.) Moreover, according to Dr. Blume, dechallenge and rechallenge

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[65] As defined by the FDA in a guidance document, a "safety signal":

> refers to a concern about an excess of adverse events compared to what would be expected to be associated with a product's use. Signals can arise from postmarketing data and other sources, such as preclinical data and events associated with other products in the same pharmacologic class . . . . Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the product caused the event.

U.S. Dept. of Heath and Human Services, Food and Drug Administration, Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiolgic Assessment 4 (March 2005) (Pls.' Hr'g Ex. 3).

data is accepted in the field as a useful tool in making decisions as to causation. (Blume Rep. ¶¶ 55-56.)

Combing through the adverse event reports in all Neurontin clinical trials from the pre-approval stage through 1996, Dr. Blume identified forty-five positive dechallenge events. (Blume Rep. ¶¶ 58, 141.)[66] Seventeen of these events were deemed "probably" related to gabapentin, while seven were determined to be "definitely" related to gabapentin. Notably, none of these twenty-four events involved specifically suicidal behavior,[67] but rather entailed depression (one case) and "psychobiological events" such as hostility, emotional lability, thinking abnormal, nervousness, and confusion.

Dr. Blume also highlights a positive rechallenge event reported in 1991. In this event, a 36-year-old male patient experienced severe depression and suicidal ideation while on gabapentin. (1993 Med.-Stat. Review 107-08.) The depression was deemed "clinically important" and both the depression and suicidal ideations were "judged possibly related to gabapentin." (Defendants' Narrative Summaries and Tabular Data for Study Participants who Withdrew Due to Adverse Events, App'x C.3, at

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[66] A series of charts cataloguing the identified events follow ¶ 141 of Blume's Report.

[67] In fact, only one of the forty-five positive dechallenge events involved suicidal behavior, and that instance was deemed "definitely not" related to gabapentin.

53-54) (Pls.' Ex. 91.) The patient stopped taking the drug and the depression and suicidal ideation were "resolved" (i.e., a positive dechallenge). (Id.) Approximately five months later, the patient was given gabapentin again (the "rechallenge"). The depression re-appeared just four days later, and had become "severe" within thirty days of resuming gabapentin treatment. (Id.) This time the depression was considered "probably related to gabapentin," and the patient was withdrawn from the study. (Id.)

Both Drs. Blume and Kruszewski point to this positive rechallenge patient narrative – and the dechallenge events – as significant pieces of evidence indicating a relationship between gabapentin and adverse mood and behavioral events. (See Kruszewski Rep. 14 (stating that "particular significance" should be attributed to a positive rechallenge because "such findings reflect a scientifically sound position that gabapentin was a substantial factor in causing the adverse event"); Blume Rep. ¶ 92 ("The relationship of these psychobiological adverse events to gabapentin therapy is supported by numerous examples of positive dechallenge / rechallenge data and their occurrence in a number of postmarketing surveillance databases.")).

3. Periodic Safety Update Reports

In her report, Dr. Blume extensively reviews case report data from a variety of sources beyond Defendants' own clinical

studies,[68] identifying adverse events which, in her view, collectively demonstrate "that Neurontin can be associated with suicide-related behavior." (Blume Rep. ¶ 280.) One source of such information are Periodic Safety Update Reports ("PSUR") prepared by Defendants. PSURs include "cases of adverse events reported spontaneously to Pfizer Defendants, cases reported from healthcare providers, cases published in the medical literature and cases reported from clinical studies." (Blume Rep. ¶ 162.) Notably, events are included in the PSURs regardless of causality assessments. (Id.)

After reviewing multiple PSURs for Neurontin, Dr. Blume concluded that "suicide-related adverse events . . . began to appear consistently in PSUR documents starting in 2000 and early 2001" and ultimately "culminated in large numbers of reports" in a five-year summary document issued at the beginning of 2003. (Blume Rep. ¶ 163.) In addition, Dr. Blume reviewed a PSUR covering events reported from February 2003 through January 2004, in which "gabapentin was listed as the sole suspect agent in a total of 6 completed suicides and 15 suicide attempts." (Blume Rep. ¶ 247.)

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[68] Among the sources relied on by Dr. Blume are Periodic Safety Update Reports, Defendants' Annual Reports, Adverse Event Databases, reports to the World Health Organization, Spontaneous Reporting System/Adverse Events Reporting System (SRS/AERS), the Health Canada database, and a review of the literature for reports of adverse events in patients treated with gabapentin. (Blume Rep. ¶ 161.)

4. Peer-Reviewed Literature

Case reports indicating that gabapentin can lead to mood or behavioral disturbances also appear in the peer-reviewed literature. In his report, Dr. Kruszewski cites to multiple peer reviewed articles from 1995 through 2002 which he says report adverse events that "strongly link[] gabapentin's neurobiological effects to multiple significant mood and behavioral problems." (Kruszewski Rep. 10.) Similarly, Dr. Trimble lists seven articles that report "outbursts of aggression following prescription with gabapentin," and notes that a review of anticonvulsant drugs published in 2001 commented on aggression and irritable behavior in its discussion of gabapentin. (Trimble Rep. 20.) In addition, Dr. Trimble cites a published 2002 post-marketing surveillance study of gabapentin. The study, conducted on 3,100 patients in England, reported 311 psychiatric events, including fifty depression, forty-one aggression, twenty-eight anxiety, twenty-seven abnormal behavior, and twenty-six confusion. The authors noted that seventeen patients took an overdose and two patients made suicide threats. (Trimble Rep. 37-38.)

5. Trimble's Research for Defendants

Finally, Dr. Trimble's research for Defendants back in 1996 provides additional data worthy of consideration. Dr. Trimble reviewed a total seventy-six case reports of psychosis, mood

disturbances, and aggressive behavior in patients taking Neurontin. Dr. Trimble concluded that nine of the twenty-one cases of aggression (forty-three percent) were either precipitated or exacerbated by gabapentin. (Behavioural Disturbance with Gabapentin 13.) As for depression, Dr. Trimble reported that there was a possible association in two of ten cases he examined in detail, but concluded that it was "not possible to clearly link gabapentin with any case directly."[69] (Id. at 14.)

Despite Defendants' insistence to the contrary, adverse event reports of behaviors which are not directly suicidal, such as depression and aggression, are relevant to the ultimate inquiry because Plaintiffs' theory is that Neurontin causes a decrease in serotonin in a patient's brain which, in turn, can prompt mood and behavioral disturbances, some of which ultimately lead to suicidal behavior.[70]

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[69] Dr. Trimble emphasized that the data was often incomplete, particularly with respect to the case reports of depression. (Behavioural Disturbance with Gabapentin 8, 10-11.)

[70] Notably, the FDA, in its Alert, stated that various behavioral symptoms (e.g., hostility, anxiety, agitation, etc.) which themselves are not directly suicidal, "may be precursors to emerging suicidality." (FDA Alert, Jan. 31, 2008, at 2.) It is also well-established and undisputed that depression is a risk factor for suicide. (See González-Maeso, Neurotransmitter receptor-mediated activation of G-proteins in brains of suicide victims with mood disorders, 7 Molecular Psychiatry, 755, 762 (2002) ("Depression is the most important risk factor for suicide.") (Pls.' Ex. 71); (Hr'g Tr. 489, July 23, 2008 (Rothschild)) ("Depression is one of many risk factors for suicide.").

In sum, Plaintiffs' experts point to the adverse event and case report data as real-world evidence to back up their theory that Neurontin increases the risk of suicidality in its patients. As summarized by Dr. Blume: "While these events do not prove that Neurontin causes suicidal behavior, they do demonstrate, in conjunction with the vast numbers of post-marketing events, that Neurontin can be associated with suicide-related behavior." (Blume Rep. ¶ 280.)

E. Expert-Specific Challenges

Defendants contend both Drs. Kruszewski and Blume are testifying beyond their expertise when they opine on the mechanism of action of gabapentin. Defendants also contend that Dr. Blume is not qualified to offer any medical theory of causation. Defendants do not challenge Dr. Trimble's qualifications or the scope of his testimony.

Dr. Stefan Kruszewski is a board certified psychiatrist with a medical degree from Harvard Medical School, specialized training and knowledge in psychopharmacology, and twenty-eight years of clinical practice experience. (See Brief Resume, Stephan Kruszewski, M.D. (Pls.' Ex. 114); Kruszewski Aff. ¶ 1 (Pls.' Ex. 115.)) Dr. Kruszewski has been accepted as an expert witness in pharmaceutical litigation before several courts. See,

e.g., In re Zyprexa Prods. Liab. Litig., 489 F. Supp. 2d 230, 287-88 (E.D.N.Y. 2007). As a practicing psychiatrist he has treated, and prescribed drugs for, several thousand patients with a variety of psychiatric and neuropsychiatric indications. (Kruszewski Aff. ¶ 3.) Dr. Kruszewski is currently on the faculty at Eastern University in Pennsylvania and was a clinical professor of psychiatry at Pennsylvania State University from 1999-2004. He has also lectured at many universities on epidemiology, psychiatry, neuropsychiatry, and related fields. (Kruszewski Aff. ¶ 5.)

As for research activities, Dr. Kruszewski has authored articles published in peer-reviewed journals addressing issues pertaining to drugs, side-effects, conflicts of interest, and the validity and consistency of research. (Kruszewski Aff. ¶ 6.) As a member of the Board of the Alliance for Human Research Protection, Dr. Kruszewski reviews research from peer-reviewed sources discussing issues pertaining to drug side effects, including the study of side effects of anticonvulsants. (Kruszewski Aff. ¶ 7.)

Accordingly, Dr. Kruszewski is well-qualified to perform a literature search and review records of patients exposed to Neurontin, and to testify based on those investigations and his own experience as a practicing psychiatrist.

Dr. Cheryl Blume holds a Ph.D. in pharmacology and

toxicology from the West Virginia University School of Medicine. (See Curriculum Vitae of Cheryl Blume, Ph.D. (Pls.' Ex. 116.)) She has extensive experience in the evaluation of safety information of pharmaceutical products; for the past twenty-five years, Dr. Blume has worked with pharmaceutical companies to prepare new drug applications and supplemental documents for submission to the FDA. In this role, Dr. Blume has worked on at least 150 submissions to the FDA for more than fifty different drugs. (Blume Decl. ¶ 3) (Pls.' Ex. 102.) She has been involved in collecting and evaluating post-marketing adverse event reports, as well as the design of studies to assess safety signals after a drug has been approved. (Blume Rep. ¶ 3.)

Defendants contend that, despite her industry experience, Dr. Blume is not qualified to testify about Neurontin's mechanism of action or any medical theory of causation. In offering an opinion on general causation,[71] Dr. Blume does discuss mechanism of action and biological plausibility, yet her report and testimony overwhelmingly focus on the review and evaluation of adverse events associated with Neurontin. In performing this review, Dr. Blume states that she used the same methods that she employs when preparing a drug development for submission to the FDA. (Blume Decl. ¶ 5.) She states that she reviewed the same

[71] Dr. Blume also provides a failure-to-warn expert opinion, but that opinion is not at issue in this motion.

types of records and applied the same analytical methods used by the FDA to evaluate a drug's risks, benefits, safety, and efficacy. (Blume Decl. ¶ 9.)

Dr. Blume is amply qualified at least to evaluate the adverse event data and other sources of information regularly used by the FDA and industry professionals.

F. Conclusion

In a challenge to expert testimony under Daubert, the Court is tasked with operating as a gatekeeper. The court must exclude testimony that is "junk science" and rests on unreliable principles, but allow in – for a jury's evaluation – testimony that is based on "sufficient facts and data," Fed. R. Evid. 702, and "has a reliable basis in light of the knowledge and experience of the relevant discipline." Crowe, 506 F.3d at 16-17 (internal quotation marks omitted).

Here, Plaintiffs have successfully demonstrated, by a preponderance of the evidence, that their experts' general causation testimony is reliable. Most significantly, the FDA study provides evidence of an association between Neurontin and an increased risk of suicidality, the prerequisite for a causation analysis under the Bradford Hill criteria. Though the parties' experts debate the strength and specificity of the association (two Bradford Hill factors), its presence alone significantly strengthens the Plaintiffs' case for admission

under Daubert.

Moreover, Plaintiffs have demonstrated that a relationship between gabapentin and increased suicidality is biologically plausible, a particularly crucial Bradford Hill factor. That a decrease in serotonin and other monoamines can lead to negative effects on mood and behavior, and even prompt suicidality, is well established and hardly disputed by Defendants. What is hotly disputed is whether gabapentin causes any such decrease in monoamines. In this battle, both sides present peer-reviewed studies to support their position. Plaintiffs' star expert Dr. Trimble relies primarily on in vitro animal studies and a mechanism of action theory that is questioned by some in the scientific community. Yet, Dr. Trimble has more than animal studies on which to rest his theory – there is a long trail of "gabapentin as GABAergic" literature winding from Defendants' own doorstep to the halls of the FDA. Dr. Trimble is an exceptionally well-qualified individual who has applied methods generally accepted in his field. His testimony rests on "good grounds, based on what is known." Ruiz-Troche, 161 F.3d at 85 (quoting Daubert, 509 U.S. at 590). Accordingly, disputes over his theory of biological plausibility "should be tested by the adversary process – competing expert testimony and active cross-examination – rather than excluded from a jury's scrutiny." Id.

Finally, the remaining Bradford Hill factors were not the

focal point of either the briefing or the three days of hearing testimony, though several additional factors were touched upon. As for consistency, or replication of findings, both parties agreed that the FDA meta-analysis was the first of its kind and has not been repeated. Thus, there is little evidence either way for this factor. The case report data, particularly the dechallenge and rechallenge data, provides some evidence of a temporal relationship between taking gabapentin and the alleged adverse effects, while Plaintiffs' experts' analogies to other GABAergic antiepileptic drugs, some of which are known to be associated with negative effects on mood and behavior, also support an inference of causation. And although there is dispute within the scientific field as to the chemical and pharmacological properties of gabapentin, the proposition that gabapentin increases the risk of suicidal behavior by decreasing serotonin in the human brain is consistent with "generally known facts" about the causes of suicidality.[72]

In sum, Plaintiffs have demonstrated that their experts' theory of general causation is admissible under Daubert and

[72] As for the remaining factors, the dose response relationship was not emphasized by either Plaintiffs or Defendants. It is not clear to this Court whether "experiment" encompasses observations such as dechallenge / rechallenge data or whether it solely refers to structured studies testing a particular hypothesis. Either way, this factor is arguably subsumed into the discussion of consistency or temporal relationship above.

Federal Rule of Evidence 702.

IV. ORDER

The Motion to Exclude Plaintiffs' experts' testimony on general causation (Docket No. 1157) is **DENIED**.

S/PATTI B. SARIS
United States District Judge

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Note* This page is not part of the opinion as entered by the court.

The docket information provided on this page is for the benefit

of publishers of these opinions.

Attorneys

Reema Abdelhamid Davis Polk & Wardwell 450 Lexington Avenue New York, NY 10017 212-450-4066 212-450-3066 (fax) reema.abdelhamid@gmail.com Assigned: 09/15/2005 TERMINATED: 03/10/2006 ATTORNEY TO BE NOTICED	representing	Pfizer, Inc. (Defendant)
Terry P Abeyta Abeyta Nelson 1102 West Yakima Avenue Yakima, WA 98902-3029 509-575-1588 509-457-8426 (fax) Assigned: 08/22/2006 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Nicole Y Campbell (Consolidated Plaintiff) Ricka Leah Westfall (Consolidated Plaintiff) Joy M. Shaw (Consolidated Plaintiff)
John C. Aisenbrey Stinson Morrison Hecker, LLP 1201 Walnut Street Kansas City, MO 64106-2150 816-842-8600 816-691-3495 (fax)	representing	Parke-Davis (Defendant)

jaisenbrey@stinsonmoheck.com

Assigned: 11/07/2005 TERMINATED:

04/11/2007 LEAD ATTORNEY

ATTORNEY TO BE NOTICED

William A. Alford, III SHOOK HARDY & BACON 2555 Grand Boulevard Kansas City, MO 64108-2613 816/474-6550 816/421-5547 (fax) Assigned: 06/20/2008 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Pfizer, Inc. (Defendant) Parke-Davis (Defendant)
Keith L. Altman Finkelstein & Partners, LLP 1279 Route 300 Newburgh, NY 12551 516-456-5885 kaltman@lawampmmt.com Assigned: 12/12/2008 LEAD ATTORNEY PRO HAC VICE ATTORNEY TO BE NOTICED	representing	Pfizer, Inc. (Consolidated Defendant) Warner-Lambert Company (Defendant) Warner-Lambert Company LLC (Defendant) Members of the Plaintiffs Product Liability Steering Committee (Plaintiff)
Leasa M. W. Anderson Blank Rome LP 600 New Hampshire Avenue, NW Washington, DC 20037 202-772-5970 202-772-1691 (fax) Assigned: 01/15/2009 LEAD ATTORNEY PRO HAC VICE ATTORNEY TO BE NOTICED	representing	Third Party Payors (Plaintiff)
Scott William Anderson Shook Hardy & Bacon, L.L.P 100 N. Tampa Street Suite 2900 Tampa, FL 33602 813-202-	representing	Pfizer, Inc. (Defendant)

7100 813-221-8837 (fax) Assigned:

12/07/2005 TERMINATED: 04/11/2007

LEAD ATTORNEY ATTORNEY TO BE

NOTICED

		Parke-Davis (Defendant) Warner-Lambert Company (Defendant) Warner-Lambert Company LLC (Defendant) Pfizer, Inc. (Consolidated Defendant)
Ray M. Aragon McKenna Long &	representi	Actavis Elizabeth LLC (Consolidated Defendant)
Aldridge LLP 1900 K Street, N.W.	ng	
Washington, DC 20006 202-496-7500		
Assigned: 07/19/2007 LEAD ATTORNEY		
ATTORNEY TO BE NOTICED		
		Actavis Inc. (Consolidated Defendant) Purepac Pharmaceutical Co. (Consolidated Defendant)
Ronald Judah Aranoff Bernstein	representi	Lorraine Kopa (Consolidated Plaintiff)
Liebhard LLP 10 East 40th Street New	ng	
York, NY 07666 212-779-1414 212-		
779-3218 (fax) aranoff@bernlieb.com		
Assigned: 05/26/2005 LEAD ATTORNEY		
ATTORNEY TO BE NOTICED		
Bryan Frederick Aylstock Aylstock,	representi	Curtis Durden, Jr. (Consolidated Plaintiff)
Witkin, Kreis & Overholtz, PLLC 803 N	ng	
Palafox St Pensacola, FL 32501		
850/916-7450 Ext 36 850/916-7449		
(fax) Assigned: 10/07/2008 LEAD		
ATTORNEY ATTORNEY TO BE		
NOTICED		
		Lori Durden (Consolidated Plaintiff)
Laureen Furey Bagley Sloan & Monsour	representi	Linda Barker TERMINATED: 01/29/2008
101 East Whaley Street Longview, TX	ng	(Consolidated Plaintiff)
75606 903-757-7000 903-757-7574		

(fax) lbagley@sloanmonsour.com Assigned: 11/02/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED		
Jeffrey R. Baker PO Box 650 Jackson, MS 39205-0650 601-948-6470 Assigned: 03/07/2006 TERMINATED: 04/11/2007 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Pfizer, Inc. (Defendant)
Gordon Ball Ball & Scott Bank of America Building Suite 750 550 W. Main Avenue Knoxville, TN 37902 865-525-7028 865-525-4679 (fax) filings@ballandscott.com Assigned: 03/03/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Bauda VL Sutton Ball & Scott 550 W. Main Ave. Knoxville, TN 37902 865-525-7028 865-525-4679 (fax) filings@ballandscott.com (Plaintiff)
Richard M. Barnes Goodell DeVries Leech & Dann, LLP One South Street 20th Floor Baltimore, MD 21202 410-783-4000 Assigned: 06/30/2008 LEAD ATTORNEY PRO HAC VICE ATTORNEY TO BE NOTICED	representing	Parke-Davis (Defendant)
Catherine Marie Valerio Barrad Sidley Austin, LLP 555 West Fifth Street Suite 4000 Los Angeles, CA 90013 213-896-6600 213-896-660 (fax) Assigned: 03/28/2006 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Pfizer, Inc. (Consolidated Defendant) Pfizer, Inc. (Defendant) Warner-Lambert Company (Defendant) Warner-Lambert Company LLC (Defendant) Parke-Davis (Defendant)
		Pfizer, Inc. (Defendant)

		Warner-Lambert Company (Defendant) Warner-Lambert Company LLC (Defendant)
Charles F. Barrett Barrett & Associates PA 6518 Highway 100 Suite 210 Nashville, TN 37205 615-515-3393 615-515-3395 (fax) cb@barrettandassociates.net Assigned: 10/28/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Mary Lou Lienerth (Consolidated Defendant)
		Ruth Smith (Consolidated Plaintiff) Steven Michielsen (Consolidated Plaintiff)
Don Barrett Barrett Law Office 404 Court Square North PO Box 987 Lexington, MS 39095 662-834-2376 662-834-2628 (fax) dbarrett@barrettlawoffice.com Assigned: 12/17/2004 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Harden Manufacturing Corporation (Plaintiff)
		Members of the Class Plaintiffs Steering Committee (Plaintiff) Mary Lou Lienerth (Consolidated Defendant)
Thomas F. Basile The Calwell Practice PO Box 113 Charleston, WV 25321-0113 304-343-4323 Assigned: 03/28/2006 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Donald Walker (Consolidated Plaintiff)
		Donna Joyce Adkins (Consolidated Plaintiff)
Bradley Douglas Becnel Law offices of Daniel E. Becnel, Jr. 106 W. Seventh Street PO Drawer H Reserve, LA 70084 985-536-1186 985-536-6445 (fax) Assigned: 10/04/2005 LEAD	representing	Emma B. Christina (Consolidated Plaintiff)

ATTORNEY ATTORNEY TO BE

NOTICED

Daniel E. Becnel, Jr. Becnel law Firm representi Harden Manufacturing Corporation (Plaintiff)

106 W. Seventh Street Reserve, LA ng

70084 985-536-1186 985-536-6445

(fax) dbecnel@becnellaw.com

Assigned: 12/17/2004 LEAD ATTORNEY

ATTORNEY TO BE NOTICED

Members of the Class Plaintiffs Steering Committee

(Plaintiff)
Emma B. Christina (Consolidated Plaintiff)
Patricia Ann White (Consolidated Plaintiff)
Harold J. McPherson (Consolidated Plaintiff)
Annie D. Blevins (Consolidated Plaintiff)

Robert M. Becnel Law Offices of Robert representi Dianne Irene Hood (Consolidated Plaintiff)

M. Becnel 425 W. Airline Highway ng

Laplace, LA 70068 985-651-6101 985-

651-6104 (fax) Assigned: 10/04/2005

LEAD ATTORNEY ATTORNEY TO BE

NOTICED

George S. Bellas Bellas & Wachowski representi Allied Services Division Welfare Fund (Consolidated

15 North Northwest Highway Park ng Plaintiff)

Ridge, IL 60068 847-823-9030

Assigned: 10/31/2005 LEAD ATTORNEY

ATTORNEY TO BE NOTICED

Richard Bemporad Lowey Dannenberg representi All Plaintiffs (All Plaintiffs)

Bemborad & Selinger, P.C. The ng

Gateway One North Broadway White

Plains, NY 10601 914-997-0500 914-

997-0035 (fax) Assigned: 02/18/2005

LEAD ATTORNEY ATTORNEY TO BE

NOTICED

		Members of the Plaintiffs Non-Class Steering Committee (Plaintiff) Aetna, Inc. (Consolidated Plaintiff)
Leslie A Benitez Clark Thomas et al PO Box 1148 Austin, TX 78767 512-472-8800 512-474-1129 (fax) Assigned: 04/18/2006 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Marcos A. Tovar (Consolidated Defendant)
		G.D. Searle, LLC (Consolidated Defendant) Mary Katriadakis TERMINATED: 08/06/2007 (Consolidated Defendant) Susan Adamo TERMINATED: 08/06/2007 (Consolidated Defendant)
Leslie Anne Benitez Clark Thomas & Winters PO Box 1148 Austin, TX 78767-1148 512-472-8800 512-495-8881 (fax) lab@ctw.com Assigned: 11/07/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Parke-Davis (Defendant) Pfizer, Inc. (Defendant)
Steve W. Berman Hagens Berman Sobol Shapiro LLP 1301 5th Avenue Suite 2900 Seattle, WA 98101-1090 206-623-7292 206-623-0594 (fax) steve@hbsslaw.com Assigned: 05/14/2004 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Harden Manufacturing Corporation (Plaintiff)
Pavel Bespalko Law Office of Joel Eigerman 50 Congress Street Suite 200 Boston, MA 02109 617-818-1982 617-523-5612 (fax) Assigned: 07/14/2006 LEAD ATTORNEY ATTORNEY TO BE	representing	The Guardian Life Insurance Company of America (Consolidated Plaintiff)

NOTICED
Robert J. Bonsignore Bonsignore & representi Laura Allen (Consolidated Plaintiff)

Brewer 23 Forest Street Medford, MA ng

02155 781-391-9400 781-391-9496

(fax) rbonsignore@class-actions.us

Assigned: 05/25/2005 LEAD ATTORNEY

ATTORNEY TO BE NOTICED

Alfred Morabito (Consolidated Plaintiff)
Timothy Bridges (Consolidated Plaintiff)

Levi Boone, III Boone Law Firm PA 401 representi Andrew Smith (Consolidated Plaintiff)

West Sunflower Avenue Cleveland, MS ng

38732-1772 662-843-7946 662-843-

7950 (fax)

LBoone@BooneLawFirm.com Assigned:

11/02/2005 LEAD ATTORNEY PRO

HAC VICE ATTORNEY TO BE

NOTICED

Annie Gatewood (Consolidated Plaintiff)
Bettie A. Newsom (Consolidated Plaintiff)
Carlene Thomas (Consolidated Plaintiff)
Charles Haynes, Jr. (Consolidated Plaintiff)
Charlotte Jenkins (Consolidated Plaintiff)
Donna M. Pierce (Consolidated Plaintiff)
Elizabeth Marie Knight (Consolidated Plaintiff)
Faith Renee Ford (Consolidated Plaintiff)
Frank Smith, Jr. (Consolidated Plaintiff)
Glinda Jean Ford (Consolidated Plaintiff)
Gregory Suber (Consolidated Plaintiff)
James Hunter (Consolidated Plaintiff)
Janie Smith (Consolidated Plaintiff)
Jerrell M. Bearden (Consolidated Plaintiff)
Jerry Lowe (Consolidated Plaintiff)
Kenneth Anthony Green (Consolidated Plaintiff)
Lee Allan Haley (Consolidated Plaintiff)
Leroy Anderson (Consolidated Plaintiff)
Lestine Rogers (Consolidated Plaintiff)
Lois Adams (Consolidated Plaintiff)
Lolita Myers (Consolidated Plaintiff)
Louisa Smith (Consolidated Plaintiff)
Marie A. Barber (Consolidated Plaintiff)
Mark Allen Prince (Consolidated Plaintiff)

		Mary Cooper (Consolidated Plaintiff) Melvin Harris (Consolidated Plaintiff) Patricia Ann Rhodes (Consolidated Plaintiff) Pearlie Maddox (Consolidated Plaintiff) Re'Shedia Young (Consolidated Plaintiff) Rodger T. Pearson (Consolidated Plaintiff) Rodney E. Plant (Consolidated Plaintiff) Roy Carrol (Consolidated Plaintiff) Shirley Drennan (Consolidated Plaintiff) Sonya Lewis (Consolidated Plaintiff) Sue Beckum (Consolidated Plaintiff) Warren Nancy (Consolidated Plaintiff) William Webb (Consolidated Plaintiff) Dorothy Lott TERMINATED: 12/15/2008 (Consolidated Plaintiff) Shirley Torry Martin TERMINATED: 12/15/2008 (Consolidated Plaintiff) Jessie Allen (Consolidated Plaintiff)
Rainey Cawthon Booth Littlepage & Booth 331 E. Romana Street Pensacola, FL 32502 850-432-1500 850-432-1505 (fax) Assigned: 03/07/2006 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Donna Sims (Consolidated Plaintiff)
		John Owens (Consolidated Plaintiff)
Walter L. Boyaki Miranda & Boyaki 4621 Pershing Drive El Paso, TX 79903 915-566-8688 915-566-5906 (fax) Wboyaki@aol.com Assigned: 06/22/2007 LEAD ATTORNEY PRO HAC VICE ATTORNEY TO BE NOTICED	representing	Gloria Telles (Consolidated Plaintiff)
John A. Boyle Marino & Associates One Newark Center 9th Floor Newark, NJ 07102-5211 973-783-2343 jboyle@khmarino.com Assigned: 11/02/2005 LEAD ATTORNEY	representing	Cline, Davis & Mann, Inc. (Consolidated Defendant)

ATTORNEY TO BE NOTICED

Derek T. Braslow Pogust & Braslow LLC 161 Washington Street Suite 1520 Conshohocken, PA 19428 610-941-4204 610-941-4245 (fax) Assigned: 05/23/2006 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Jennifer Flanders (Consolidated Plaintiff)
		Anne Ellis (Consolidated Plaintiff) Howard Ellis (Consolidated Plaintiff) Dale Wayne Henderson (Consolidated Plaintiff) Early Cox (Consolidated Plaintiff) Sharon Cox (Consolidated Plaintiff) Daniel Newberry (Consolidated Plaintiff) Erik Newberry (Consolidated Plaintiff) Holly Newberry (Consolidated Plaintiff) ALICE HAIRFIELD (Consolidated Plaintiff)
Eugene Brooks Brooks Law Firm P.O. Box 9545 313 West York Street Savannah, GA 31401 912-233-9696 912-232-8620 (fax) gbrooks@brooks-law.com Assigned: 10/11/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Deidre R. Rodriguez (Consolidated Plaintiff)
		Jack C. Reeves, Jr. (Consolidated Plaintiff) Kelly Strickland (Consolidated Plaintiff) Kelly R. Strickland (Consolidated Plaintiff)
William L. Bross Heninger, Garrison & Davis, LLC 2224 First Avenue North PO Box 11310 Birmingham, AL 35202 205-326-3336 205-326-3332 (fax) wlbross@hgdlawfirm.com Assigned: 08/10/2006 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Charles Brown (Consolidated Plaintiff)
		Jacqueline Poole (Consolidated Plaintiff) Jessica Whitten (Consolidated Plaintiff) Joyce Reach (Consolidated Plaintiff)

Leisa Eaddy (Consolidated Plaintiff)
Marsha Holloway (Consolidated Plaintiff)
Meicki Baker (Consolidated Plaintiff)
Odessa Grissom (Consolidated Plaintiff)
Pauline Huff (Consolidated Plaintiff)
Shelia Agee (Consolidated Plaintiff)
Troy Chappell (Consolidated Plaintiff)

David L. Browne Dugan & Browne, PLC 650 Poydras Street Suite 2150 New Orleans, LA 70130 504-648-0180 504-648-0181 (fax) Assigned: 06/14/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED — representing: Louisiana Health Service Indemnity Company (Plaintiff)

Carol D. Browning Stites & Harbison 400 W. Market Street Suite 1800 Louisville, KY 40202-3352 502-587-3400 502-587-6391 (fax) Assigned: 10/31/2005 TERMINATED: 04/11/2007 LEAD ATTORNEY ATTORNEY TO BE NOTICED — representing: Pfizer, Inc. (Defendant)

Joseph M. Bruno Bruno & Bruno LLP 855 Baronne Street New Orleans, LA 70113 504-525-1335 504-561-6775 (fax) JBruno@brunobrunolaw.com Assigned: 10/04/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED — representing: Debra Mull (Consolidated Plaintiff)

Stephanie M. Bruno Bruno & Bruno 855 Baronne Street New Orleans, LA 70113 504-525-1335 504-581-1493 (fax) Assigned: 10/04/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED — representing: Debra Mull (Consolidated Plaintiff)

Susan E. Burnett Clark Thomas & Winters PO Box 1148 Austin, TX — representing: Parke-Davis (Defendant)

78767-1148 512-472-8800 512-495-

8881 (fax) seb@ctw.com Assigned:

11/07/2005 LEAD ATTORNEY

ATTORNEY TO BE NOTICED

		Pfizer, Inc. (Defendant) Marcos A. Tovar (Consolidated Defendant)
Carter H. Burwell Davis Polk & Wardwell 450 Lexington Avenue New York, NY 10017 212-450-4000 Assigned: 09/29/2005 ATTORNEY TO BE NOTICED	representing	Pfizer, Inc. (Defendant)
Philip Henry Butler Bradley, Arant, Rose & White LLP Suite 780 401 Adams Avenue Montgomery, AL 36104 334-956-7602 334-956-7701 (fax) pbutler@bradleyarant.com Assigned: 10/28/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Pfizer, Inc. (Defendant)
W. Stuart Calwell The Calwell Practice PLLC PO Box 113 Charleston, WV 25321-0113 304-343-4323 Assigned: 03/28/2006 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Donald Walker (Consolidated Plaintiff)
		Donna Joyce Adkins (Consolidated Plaintiff) Michael L. Malcolm (Consolidated Plaintiff) Sandra Lynn Messer (Consolidated Plaintiff)
Andrew P. Campbell Campbell Waller & Poer LLC 2100-A Southbridge Parkway Birmingham, AL 35209-1303 205-803-0051 205-803-0053 (fax) acampbell@cwp-law.com Assigned: 10/28/2005 LEAD ATTORNEY	representing	Alabama Forest Products Industry Workmen's Compensation Self-Insurer's Fund (Consolidated Plaintiff)

ATTORNEY TO BE NOTICED
David C. Campbell Williams Kastner & Gibbs, PLLC 888 SW Fifth Avenue Portland, OR 97204-2025 503-944-6967 503-222-7261 (fax) dcampbell@wkg.com Assigned: 10/26/2005 TERMINATED: 04/11/2007 LEAD ATTORNEY ATTORNEY TO BE NOTICED — representing: Parke-Davis (Defendant)

Ronald J. Campione Budd Larner, PC 150 John F. Kennedy Parkway CN1000 Short Hills, NJ 07078-0999 973-379-4800 rcampione@budd-larner.com Assigned: 11/02/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED — representing: Pfizer, Inc. (Defendant); Assurant Health, Inc. (Consolidated Plaintiff)

John E. Caruso Montgomery, McCracken, Walker & Rhoads Liberty View 457 Haddonfield Rd. Cherry Hill, NJ 08002 856-488-7700 jcaruso@mmwr.com Assigned: 10/18/2005 TERMINATED: 04/11/2007 LEAD ATTORNEY ATTORNEY TO BE NOTICED — representing: Parke-Davis (Defendant); Pfizer, Inc. (Defendant)

David B. Chaffin White and Williams LLP 100 Summer Street Suite 2707 Boston, MA 02110-1701 617-748-5200 617-748-5201 (fax) chaffind@whiteandwilliams.com — representing: Parke-Davis (Defendant)

Assigned: 07/15/2004 LEAD ATTORNEY		
ATTORNEY TO BE NOTICED		
		Pfizer, Inc. (Defendant) Pfizer, Inc. (Consolidated Defendant) Andrew W. Wallace (Consolidated Defendant)
Prince C. Chambliss, Jr. Stokes,	representi	Pfizer, Inc. (Defendant)
Bartholomew, Evans, & Petree, P.A.	ng	
1000 Ridgeway Loop Road Memphis,		
TN 38120 901-525-6781 Assigned:		
10/28/2005 TERMINATED: 04/11/2007		
LEAD ATTORNEY ATTORNEY TO BE		
NOTICED		
Kathleen C. Chavez 1110 Appleton	representi	Leonard Olsen (Consolidated Plaintiff)
Lane Geneva, IL 60134 630-845-3044	ng	
GKEG4@aol.com Assigned: 10/31/2005		
LEAD ATTORNEY ATTORNEY TO BE		
NOTICED		
Mark S. Cheffo Skadden, Arps, Slate,	representi	Parke-Davis (Defendant)
Meagher & Flom LLP Four Times	ng	
Square New York, NY 10036 212-735-		
3000 mark.cheffo@skadden.com		
Assigned: 04/01/2009 LEAD ATTORNEY		
ATTORNEY TO BE NOTICED		
		Pfizer, Inc. (Consolidated Defendant) Pfizer, Inc. (Defendant) Warner-Lambert Company (Defendant) Warner-Lambert Company LLC (Defendant)
Julia Pai-Yun Cheng Beam Brobeck	representi	D.O. James P. Hall Beam, Brobeck, West, Borges
West Borges and Rosa LLP 600 West	ng	& Rosa, LLP 600 W. Santa Ana Blvd. Suite 1000
Santa Ana Boulevard Santa Ana, CA		Santa Ana, CA 92701 (714) 558-3944 (714) 568-
92701-4586 714-558-3944 714-568-		0129 (fax) jcheng@bbwbrlawfirm.com
0129 (fax) jcheng@bbwbrlawfirm.com		TERMINATED: 01/10/2007 (Defendant)
Assigned: 09/15/2006 TERMINATED:		

01/11/2007 ATTORNEY TO BE

NOTICED

James P Hall TERMINATED: 01/10/2007

(Consolidated Defendant)

Dane S. Ciolino Dane S. Ciolino, representi Joyce B. Duhe (Consolidated Plaintiff)

Attorney at Law P.O. Box 850848 New ng

Orleans, LA 70185-0848 504-861-5652

504-324-0143 (fax) Assigned:

10/04/2005 LEAD ATTORNEY

ATTORNEY TO BE NOTICED

Kimberly H. Clancy Sidley Austin Brown representi Parke-Davis (Defendant)

& Wood LLP 555 West Fifith Street ng

Suite 4000 Los Angeles, CA 90013-

1010 213-896-6000 213-896-6600 (fax)

Assigned: 10/18/2005 LEAD ATTORNEY

ATTORNEY TO BE NOTICED

Pfizer, Inc. (Defendant)

Robert A. Clifford Clifford Law Offices, representi Allied Services Division Welfare Fund (Consolidated

P.C. 120 North LaSalle Street Chicago, ng Plaintiff)

IL 60602 312-899-9090 Assigned:

10/31/2005 LEAD ATTORNEY

ATTORNEY TO BE NOTICED

John R. Climaco Climaco Lefkowitz representi Harold J. McPherson (Consolidated Plaintiff)

Peca Wilcox & Garofoli 900 Halle Bldg. ng

1228 Euclid Ave. Cleveland, OH 44115

216-621-8484 216-771-1632 (fax)

jrclim@climacolaw.com Assigned:

10/18/2005 LEAD ATTORNEY

ATTORNEY TO BE NOTICED

Daniel M. Cohen Cuneo Gilbert & representi Judy Morris (Consolidated Plaintiff)

LaDuca 507 C Street, NE Washington, ng

DC 20002 202-441-9724 202-789-1813

(fax) Assigned: 05/02/2006 LEAD

ATTORNEY ATTORNEY TO BE

NOTICED

		David Huff (Consolidated Plaintiff) Daniel Johnson (Consolidated Plaintiff) Susan Johnson (Consolidated Plaintiff) Early Cox (Consolidated Plaintiff) Sharon Cox (Consolidated Plaintiff) Dorothy Beckworth (Consolidated Plaintiff) Robert Beckworth (Consolidated Plaintiff) Pamela Woolum (Consolidated Plaintiff) Richard Woolum (Consolidated Plaintiff) Deborah Valentine (Consolidated Plaintiff)
Richard W. Cohen Lowey Dannenberg Bemporad & Slelinger, P.C. One North Broadway Suite 509 White Plains, NY 10601-1714 914-997-0500 914-997-0035 (fax) rcohen@lowey.com Assigned: 12/17/2004 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Harden Manufacturing Corporation (Plaintiff)
		Aetna, Inc. (Consolidated Plaintiff)
Jonathan S. Coleman Johnson, Pope, Okor, Ruppel & Burns LLP 403 East Madison St. Tampa, FL 33602 813-225-2500 813-223-7118 (fax) jonathanc@jpfirm.com Assigned: 08/19/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Ana Medero (Plaintiff)
		Shirley Levin (Plaintiff)
John A. Commerford Meyers Taber & Meyers PC 2415 E Camelback Road Suite 900 Phoenix, AZ 85016 602-468-8900 Assigned: 10/18/2005 LEAD ATTORNEY ATTORNEY TO BE	representing	Melissa Johnson (Consolidated Plaintiff)

NOTICED

Charles Horne Cooper, Jr. Cooper & Elliott 2175 Riverside Drive Columbus, OH 43221 614-481-6000 614-481-6001 (fax) chipc@cooperelliott.com Assigned: 11/01/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED — representing: Rebecca Groves (Consolidated Plaintiff)

Susan G. Copeland Law Office of J. Doyle Fuller 2851 Zelda Road Montgomery, AL 36106 334-270-0020 334-270-9848 (fax) susanc@jdoylefuller.com Assigned: 10/28/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED — representing: Alabama Forest Products Industry Workmen's Compensation Self-Insurer's Fund (Consolidated Plaintiff)

W. Lloyd Copeland Taylor, Martino & Hedge, P.C. Post Office Box 894 Mobile, AL 36601 334-433-3131 Assigned: 10/03/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED — representing: Gulf Distributing Holdings, LLC (Consolidated Plaintiff)

Angel Blount (Consolidated Plaintiff)
Cliff Champagne (Consolidated Plaintiff)
Herman Ward (Consolidated Plaintiff)
James M. Harpring (Consolidated Plaintiff)
Nancy Coleman (Consolidated Plaintiff)
Paul Verzone (Consolidated Plaintiff)
Susan Mathey (Consolidated Plaintiff)

S. Tessie Corbin 1717 Arch Street 4000 Bell Atlantic Tower Philadelphia, PA 19103-2793 215-994-4000 Assigned: 03/28/2006 TERMINATED: 04/11/2007 LEAD ATTORNEY ATTORNEY TO BE NOTICED — representing: Parke-Davis (Defendant)

Pfizer, Inc. (Defendant)

		Warner-Lambert Company (Defendant) Warner-Lambert Company LLC (Defendant)
Paul F. Corcoran Davis & GIlbert LLP 1740 Broadway New York, NY 10019 212-468-4825 212-974-7037 (fax) pcorcoran@dglaw.com Assigned: 05/12/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Cline, Davis & Mann, Inc. (Consolidated Defendant)
Ian Crawford Todd & Weld LLP 28 State Street 31st Floor Boston, MA 02109 617-720-2626 617-227-5777 (fax) icrawford@toddweld.com Assigned: 02/20/2007 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	IMS Health Inc. (Intervenor)
Sarah G. Cronan Stites & Harbison, PLLC 400 W. Market Street Suite 1800 Louisville, KY 40202-3352 502-681- 0543 502-587-6391 (fax) Assigned: 10/31/2005 TERMINATED: 04/11/2007 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Pfizer, Inc. (Defendant)
Silas G. Cross, Jr. Cross, Poole & Smith, LLC 1416 Greensboro Avenue Tuscaloosa, AL 35401 205-391-9932 dcross@cpgf-law.com Assigned: 11/07/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Frieda Burroughs (Consolidated Plaintiff)
Rebecca Cunard Cunard Law Firm 9214 Interline Avenue Baton Rouge, LA 70809 225-925-2978 225-925-8192	representing	Linda Rizzo (Consolidated Plaintiff)

(fax) Assigned: 10/31/2005 LEAD

ATTORNEY ATTORNEY TO BE

NOTICED

Daniel D'Angelo Gilman and Pastor, LLP 63 Atlantic Avenue 3rd Floor Boston, MA 02110 617-742-9700 617-742-9701 (fax) Ddangelo@gilmanpastor.com Assigned: 05/25/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Laura Allen (Consolidated Plaintiff) Alfred Morabito (Consolidated Plaintiff) Timothy Bridges (Consolidated Plaintiff)
Jeanne F. D'Esposito Lowey Dannenberg Bemporad & Selinger, P.C. The Gateway - 11th Floor One North Lexington Avenue White Plains, NY 10601-1714 914-997-0500 914-997-0035 (fax) Assigned: 07/14/2006 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Aetna, Inc. (Consolidated Plaintiff)
EVAN W. DAVIS DECHERT LLP CIRA CENTRE 2929 ARCH ST PHILA, PA 19104 215/994-2565 Assigned: 06/02/2008 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Parke-Davis (Defendant) Pfizer, Inc. (Consolidated Defendant) Warner-Lambert Company (Defendant) Warner-Lambert Company LLC (Defendant)
Annamarie A. Daley Robins, Kaplan, Miller & Ciresi LLP 2800 LaSalle Plaza 800 LaSalle Avenue Minneapolis, MN 55402-2015 612-349-8431 612-339-	representing	Assurant Health, Inc. (Consolidated Plaintiff)

4181 (fax) aadaley@rkmc.com Assigned: 11/02/2005 TERMINATED: 06/30/2008 LEAD ATTORNEY ATTORNEY TO BE NOTICED		Assurant Plaintiffs (Plaintiff)
Michael A K Dan Michael A K Dan Law Office 1990 South Bundy Drive Suite 540 Los Angeles, CA 90210 310-979- 0325 Assigned: 08/10/2006 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representi ng	Harry Lewis TERMINATED: 12/11/2006 (Consolidated Plaintiff)
		Marilyn Lewis TERMINATED: 12/11/2006 (Consolidated Plaintiff)
Timothy C Davis Heninger, Garrison & Davis, LLC 2224 First Avenue North PO Box 11310 Birmingham, AL 35202 205-326-3336 205-326-3332 (fax) Assigned: 08/10/2006 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representi ng	Charles Brown (Consolidated Plaintiff)
		Jacqueline Poole (Consolidated Plaintiff) Jessica Whitten (Consolidated Plaintiff) Joyce Reach (Consolidated Plaintiff) Leisa Eaddy (Consolidated Plaintiff) Marsha Holloway (Consolidated Plaintiff) Meicki Baker (Consolidated Plaintiff) Odessa Grissom (Consolidated Plaintiff) Pauline Huff (Consolidated Plaintiff) Shelia Agee (Consolidated Plaintiff) Troy Chappell (Consolidated Plaintiff)
Samuel J. DeMaio Girards Law Firm 10000 N Central Expwy Suite 750 Dallas, TX 75231 214-346-9529 Assigned: 11/07/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representi ng	Steven Alexander (Consolidated Plaintiff)
Neil A. Dean Rice, Dean & Kelsey LLC	representi	Brenda Cunningham (Consolidated Plaintiff)

214 SW 6th Street Suite 305 Topeka, KS 66603 785-357-0333 x109 785-357-0216 (fax) ndean@rdk.kscoxmail.com Assigned: 11/07/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED	ng	
Christopher Brooks Dellmuth 2971 Rumson Drive Harrisburg, PA 17104 717-233-7007 717-233-7007 (fax) cbrooks221@comcast.net Assigned: 02/06/2008 LEAD ATTORNEY PRO HAC VICE ATTORNEY TO BE NOTICED	representing	Grace Sanutti (Consolidated Plaintiff)
Dimple Harendra Desai Law Office of Dimple H. Desai 5216 Westshire Lane Dallas, TX 75287 972-735-8181 Assigned: 05/01/2006 TERMINATED: 04/11/2007 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Parke-Davis (Defendant)
Charles H. Dodson, Jr. Sims, Graddick & Dodson, P.C. PO Box 1908 Mobile, AL 36633-1908 334-690-9300 251-690-9311 (fax) chd@simsgraddick.com Assigned: 10/03/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Pfizer, Inc. (Defendant) Gulf Distributing Holdings, LLC (Consolidated Plaintiff)
Thomas Marshall Donnell, Jr. Stewart,	representing	Angel Blount (Consolidated Plaintiff) Cliff Champagne (Consolidated Plaintiff) Herman Ward (Consolidated Plaintiff) James M. Harpring (Consolidated Plaintiff) Nancy Coleman (Consolidated Plaintiff) Paul Verzone (Consolidated Plaintiff) Susan Mathey (Consolidated Plaintiff) Parke-Davis (Defendant)

Estes & Donnell Sun Trust Center 424 ng

Church Street 14th Floor Nashville, TN

37219 615-244-6538 Assigned:

02/20/2007 TERMINATED: 04/11/2007

LEAD ATTORNEY ATTORNEY TO BE

NOTICED

Pfizer, Inc. (Consolidated Defendant)
Warner-Lambert Company (Defendant)
Warner-Lambert Company LLC (Defendant)

Charles E. Dorkey, III McKenna, Long & representi Novartis Pharmaceuticals Coporation (Consolidated

Aldridge 230 Park Ave. New York, NY ng Defendant)

10169 212-905-8330 212-922-1819

(fax) Assigned: 09/09/2008 LEAD

ATTORNEY ATTORNEY TO BE

NOTICED

Sandoz, Inc. (Consolidated Defendant)

John J. Driscoll The Driscoll Firm, P.C. representi Fazila Mustafa (Consolidated Plaintiff)

211 N. Broadway Ste. 2440 St. Louis, ng

MO 63102 314-932-3232 314-932-3233

(fax) john@dchelps.com Assigned:

08/10/2006 LEAD ATTORNEY

ATTORNEY TO BE NOTICED

Mohammad Mustafa (Consolidated Plaintiff)

Paul R. Duden Williams Kastner & representi Parke-Davis (Defendant)

Gibbs, PLLC 888 SW Fifth Avenue Suit ng

600 Portland, OR 97204-2025 503-228-

7967 503-222-7261 (fax)

pduden@wkg.com Assigned: 10/26/2005

TERMINATED: 04/11/2007 LEAD

ATTORNEY ATTORNEY TO BE

NOTICED

Pfizer, Inc. (Defendant)

		Warner-Lambert Company (Defendant) Warner-Lambert Company LLC (Defendant)
James R. Dugan, II Dugan & Browne PLC 650 Poydras St Suite 2150 New Orleans, LA 70130 504-648-0180 504-648-0181 (fax) jdugan@dugan-lawfirm.com Assigned: 12/17/2004 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Harden Manufacturing Corporation (Plaintiff)
James R. Dugan, II Murray Law Firm 650 Poydras Street Suite 2150 New Orleans, LA 70130 504-648-0180 Assigned: 06/14/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Allied Services Division Welfare Fund (Consolidated Plaintiff)
		Louisiana Health Service Indemnity Company (Plaintiff)
		Members of the Class Plaintiffs Steering Committee (Plaintiff)
James T. Dulin Dulin & Dulin PO Box 820 Gulfport, MS 39502 228-864-7588 Assigned: 02/21/2007 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Hilda Bonner (Consolidated Plaintiff)
J Blake Dutcher, Jr Godlove Joyner Mayall Dzialo Dutcher & Erwin PO Box 29 Lawton, OK 73502 580-353-6700 580-353-2900 (fax) Assigned: 10/24/2006 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Larry A. Shelley (Consolidated Plaintiff)
Daniel J. Dwyer Hanify & King Professional Corporation One Beacon Street Boston, MA 02108-3107 617-	representing	Anthony Wild (Defendant)

423-0400 617-423-0498 (fax) djd@hanify.com Assigned: 05/12/2005 ATTORNEY TO BE NOTICED		
Scott A. Edelman Milbank, Tweed, Hadley & McCloy LLP 1 Chase Manhattan Plaza New York, NY 10005-1413 212-530-5149 Assigned: 05/18/2007 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Lodewijk J.R. DeVink (Defendant) Anthony Wild (Defendant)
Donald S. Edgar Law Office of Donald S. Edgar 408 College Avenue Santa Rosa, CA 95401 707-545-3200 707-578-3040 (fax) don@classattorneys.com Assigned: 03/28/2006 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Lodewijk J.R. DeVink (Defendant) Charles K. Smith (Consolidated Plaintiff)
Mark L. Edwards Stipe Law Firm 343 E. Carl Albert McAlester, OK 74501 918-423-0421 918-423-0266 (fax) medwards@edwardslawok.com Assigned: 10/31/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Ricky E. Smith (Consolidated Plaintiff) Rosemary Smith (Consolidated Plaintiff) Jeffrey Mecija (Consolidated Plaintiff) Jennifer Mecija (Consolidated Plaintiff) Carolyn Hollaway (Consolidated Plaintiff)
Tony W. Edwards P.O. Box 1369 McAlester, OK 74502 918-423-0421 Assigned: 10/31/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Jerry Hollaway (Consolidated Plaintiff) Carolyn Hollaway (Consolidated Plaintiff)

Wanda Jean Edwards Fayard & Honeycutt 519 Florida Boulevard Denham Springs, LA 70726 225-664-4193 225-664-6925 (fax) Assigned: 10/31/2005 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Jerry Hollaway (Consolidated Plaintiff) Barbara M. Strawitz (Consolidated Plaintiff)
Joel Z. Eigerman Joel Z. Eigerman, Attorney-at-Law Suite 200 50 Congress Street Boston, MA 02109 617-523-3050 617-523-3050 (fax) joel@eigerman.com Assigned: 07/14/2006 LEAD ATTORNEY ATTORNEY TO BE NOTICED	representing	Elaine Lucille Edwards (Consolidated Plaintiff) Susan Roby (Consolidated Plaintiff) Tracey Lynn Robichaux (Consolidated Plaintiff) The Guardian Life Insurance Company of America (Consolidated Plaintiff)

Richard Mark Eldridge Eldridge Cooper Steichen & Leach PLLC P.O. Box 3566 Tulsa, OK 74101 918-388-5555 Assigned: 10/24/2006